

ALLERGY
in Childhood

JEROME GLASER, M.D.

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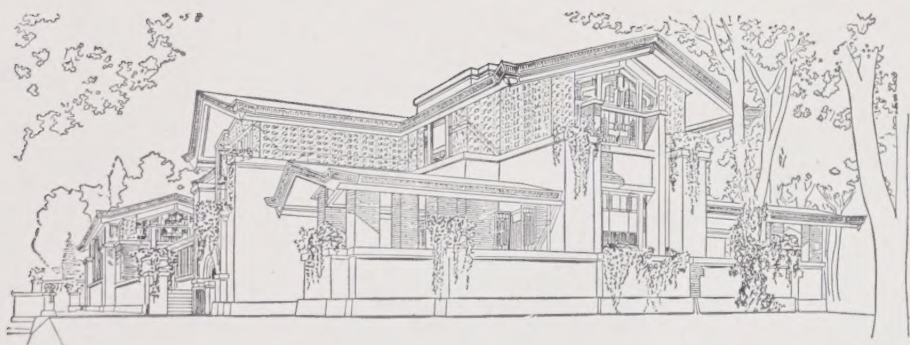
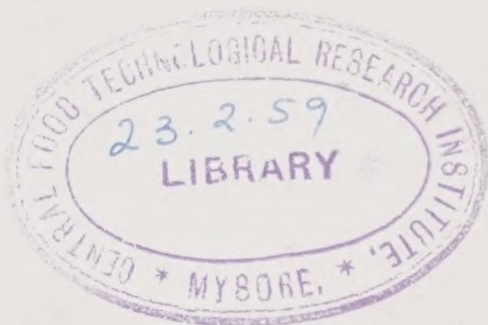
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ALLERGY IN CHILDHOOD

By

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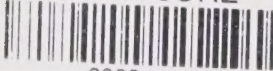
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Allergy in child

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This book is dedicated to:

My deceased father, **Simon Glaser**, for whom no sacrifice was too great if it would further the education of his children

To my wife, "**Sis**," and my sons **Fred and John**—as a poor token of compensation for the many hours of their companionship forever lost, sacrificed to the writing of this book

To the late **Dr. Samuel Wolcott Clausen**, Professor of Pediatrics at the University of Rochester School of Medicine and Dentistry, whose superior as a gentleman, a scholar and a kindly, capable physician I have never met

INTRODUCTION

IT IS NO LONGER necessary, as it was at one time, to explain why there should be specialists in internal medicine and specialists in pediatrics. These fields have developed so steadily and so extensively that it is not now possible for any one individual to be thoroughly versed in both. However, it is still true that many allergists who are internists, and this includes younger as well as older physicians, feel that there is no such thing, properly speaking, as pediatric allergy, and point with pride to the large number of children in their practices, particularly those who flock in all day Saturday for their injections of pollen or house dust extract or vaccine. However, a close examination of the makeup of such practices, as regards pediatrics, reveals that most of these patients are afflicted with typical pollinosis or typical bronchial asthma. The treatment of this is not essentially different in children, at least beyond the age of two or three years, from adults. In fact, the internist-allergist can generally treat these patients more successfully than their counterparts in adult life because they present fewer complications. Also, at this age, the tendency to spontaneous recovery is greater than in any other period of life. It may, therefore, be desirable to point out some of the essential differences between the nature of the allergy dealt with by the pediatrician and that by the internist.

First of all we have come to realize that the great majority of allergic children can be recognized very early in life. This is the time when the pediatrician, who is skilled in the diagnosis and treatment of diseases in infancy and childhood, can detect the first evidences of allergic disease. He should then take whatever steps may be necessary for its relief or modification. We are, for example, only just beginning to realize the great variety of manifestations of allergy which result from our present-day method of feeding practically all newborn infants. Cow's milk is fed instead of human breast milk or other feedings. Only the pediatrician is in a position to deal with this problem.

Another important duty of the pediatrician is the prophylaxis of allergic disease. No one in the world works harder to eliminate

the difficulties in practice which are the source of his livelihood than does the pediatrician. The pediatrician immunizes his patients routinely against all diseases in which immunization is practical. The pediatric allergist does everything he can to see that the child is raised in an environment and on a diet which inhibits the development of allergic disease. In marked contrast to this is the fact that most of today's adults (except those who were in the service) have never been immunized against tetanus by means of toxoid. Such immunization is of fundamental importance to all individuals and especially those with allergy.

Recent developments in the field of the prophylaxis of allergic disease in the newborn (to be discussed later in this book) are particularly concerned with the feeding of the newborn infant. The technical difficulties involved are such that this should be managed only by a physician who has had a good training in pediatrics and is particularly interested in newborn infants. This phase of pediatric allergy has no counterpart in the practice of the internist-allergist.

Diagnosis of bronchial asthma is much more difficult in infancy and childhood than it is in adult life because of congenital stridor and other congenital anomalies which may produce wheezing simulating asthma. On the other hand, the internist-allergist has a special problem with dyspnea of cardiac origin, certain industrial diseases such as silicosis, neoplastic diseases, and the degenerative diseases of advancing age.

The pediatric allergist is confronted not only with the problem of dosages of various medications in proportion to the weight and age of the child, but also with the paradox that such a patient may, when treated by the injection of allergenic extracts, require a dose many times larger than many an adult who has the same disease. If the allergic child becomes acutely ill the pediatrician has a special problem because of the lower bodily reserves of infancy and childhood.

This material represents the amplification of a series of lectures given in part to the medical students, and more particularly to the pediatric house staff of the Strong Memorial and Genesee Hospitals. It originated when a course in pediatric allergy was established at the University of Rochester School of Medicine and Dentistry in 1931. For the three years previous to this writing, outlines of the

lectures were mimeographed. This became such a difficult and time-consuming task that it was felt advisable to assemble the material and publish it in book form. No attempt has been made to write a complete textbook on allergy, but enough references are included so that the various phases of this subject may be studied in detail by consulting the original literature and standard textbooks of pediatrics, allergy, dermatology, and allied sciences. This book presupposes on the part of its readers a reasonable knowledge of general pediatrics. For those who wish to enter pediatric allergy, it assumes a preliminary knowledge of the subject as may be learned by working in an adult allergy clinic, or an allergy clinic dealing with both adults and children, and staffed by a competent internist-allergist and pediatrician-allergist. For this reason, this text does not go into detail concerning phases of theory and practice of allergy which are essentially the same in adults as in children, except in certain instances where this seemed desirable for the sake of clarity or emphasis.

One of the most interesting facets of pediatric allergy is that it has developed within the span of the life and practice of many men now living, i.e., it is a young specialty. In fact, it is so young that as a specialty it is sadly neglected in many of the medical schools of this country. Some department heads look upon it as scarcely more scientific than witchcraft.

The beginnings of clinical allergy go back to the observations of von Behring on reactions to antitoxin (later termed anaphylactic reactions) first used by him in the treatment of diphtheria. Some years later in 1906, von Pirquet (6) devised the term "allergy" to describe altered states of reactivity, and Schick (7), in 1913, developed the cutaneous test for susceptibility to diphtheria. However, clinical allergy, in the sense in which the word is now understood, really got its start when Schloss (8), in 1912, introduced the cutaneous scratch test with foods as a practical clinical procedure. This was closely followed by the development of the intradermal test by Cooke in 1915, as discussed by Aaron Brown (1), and other fundamental work by Walker (9) starting in 1916. Through the work of these investigators skin testing, as a diagnostic procedure for what are now known as the allergic diseases, was firmly established on a practical basis.

As in the case of the other sub-specialties in pediatrics, the pediatric allergy clinic developed out of the general pediatric clinic. As nearly as can be ascertained, the first pediatric allergy clinic was established under the direction of Dr. Edward Scott O'Keefe at the Massachussets General Hospital in January of 1918. The first publication from this clinic was by Dr. O'Keefe (4) and appeared in November of 1920. Dr. M. Murray Peshkin established a pediatric allergy clinic as part of Dr. William L. Rost's general pediatric clinic at Mt. Sinai Hospital in 1919. This grew so rapidly that in 1926 it became an autonomous unit under the same direction. The date of its first paper (5) was 1922, and in the years which followed, publications by Dr. Peshkin and the physicians trained by him covered almost all phases of allergy in children. So well was this work done that these papers still stand as authoritative documents in their field.

In 1920, Dr. Lewis Webb Hill assumed charge of a pediatric allergy clinic at Children's Hospital in Boston for a brief period of two years, and, in 1929, started a clinic for eczema in children. This led to his publishing a succession of papers which have contributed brilliantly to our knowledge, still pathetically incomplete, of this very difficult subject. During the same period, Edward S. O'Keefe and W. Ray Shannon made important contributions, and Bret Ratner began publishing a series of papers dealing with fundamental theoretical and practical problems in this field. Thus, the specialty of pediatric allergy was born.

With the growth of various boards of specialization, it was natural for a board to be established for the certification of allergists. The first to be so certified were internists who were obliged to hold the certificate of the American Board of Internal Medicine. Dr. Robert A. Cooke, the dean of American allergists, and a man who was more responsible than any other one individual for setting up the high standards required for such certification, announced this at a meeting of the then Society for the Study of Asthma and Allied Conditions at Atlantic City, New Jersey, May 2, 1942. At that time, I had the privilege of bringing up the problem of certification of pediatric allergists (3). Attention was called to the fact that it had been repeatedly pointed out in the meetings of the Society that the great majority of allergic symptoms begin at a time when the

patient is normally under the care of a pediatrician; that the pediatrician is, therefore, logically the allergist of the future, and that, as time went on and interest in pediatric allergy increased, the internists and other specialists might eventually deal mainly with the end products of neglected opportunities in pediatric allergy. Dr. Cooke urged that the pediatricians should bring pressure upon the American Board of Pediatrics to consider certification for the pediatrician allergist similar to that then being granted to internists by the American Board of Internal Medicine. However, the American Board of Pediatrics, for a long time, had very little interest in this, but, in 1945, almost entirely as a result of the efforts of Dr. Bret Ratner, this Board did announce certification in the sub-specialty of pediatric allergy (2). For its Advisory Committee on Allergy it named the same committee as the American Board of Internal Medicine with the addition of Dr. Oscar Schloss, a particularly fitting tribute to the pediatrician who initiated the clinical study of pediatric allergy. It was not, however, until October 1, 1946, that the first group of twelve pediatricians interested in allergy were certified on their records without examination by this board. In the order certified, these were: Dr. Oscar M. Schloss; Dr. Lewis Webb Hill; Dr. William P. Buffum; Dr. Bret Ratner; Dr. Jerome Glaser; Dr. Joseph H. Fries; Dr. John E. Gundy; Dr. Arthur J. Horesh; Dr. Samuel J. Levin; Dr. W. Ambrose McGee; Dr. Benjamin Zohn, and Dr. Orlando L. Ross.

The next step occurred in 1948 when a section on pediatric allergy was organized at the Atlantic City meeting of the American Academy of Pediatrics with Dr. Bert Ratner as its first chairman. Here again, a fitting tribute was paid to a pediatrician who was and is one of the leaders in the development of this specialty and in the teaching of it to others. Meantime, pediatricians were being examined for certification in the sub-specialty of allergy by a group heavily weighted with internists. The incongruity as well as the impracticality of this was soon manifest, and, in 1952, a Sub-Specialty Board of Pediatric Allergy consisting of pediatric allergists was organized by the American Board of Pediatrics. The Chairman was Dr. William P. Buffum of Providence, Rhode Island, a pediatrician distinguished for his work in asthma of early infancy, with an unquestioned reputation for fairness and ability as an organizer. In

addition, few men are so well beloved for their fine personal qualities as is Dr. Buffum by his fellow pediatricians. The following were appointed to assist him: Dr. William C. Deamer; Dr. Jerome Glaser; Dr. James C. Overall; Dr. Bret Ratner, and Dr. Albert V. Stoesser. Under this board the first examinations by pediatric allergists for pediatricians desiring certification in the sub-specialty of allergy were held in various cities under the auspices of monitors just prior to the meeting of the American Academy of Pediatrics in Chicago in October, 1952. With this event, pediatric allergy as a specialty may be said to have come of age, although it still has a struggle ahead to gain the recognition it deserves in academic and other circles.

In conclusion, I should like particularly to express my indebtedness to Dr. Samuel W. Clausen, late Professor of Pediatrics at the University of Rochester School of Medicine and Dentistry through whose cooperation I was able to start a pediatric allergy clinic there in 1931; to Dr. Stearns S. Bullen and Dr. Louis B. Baldwin (now of Phoenix, Arizona) in whose Adult Allergy Clinic I worked for a number of years before and after the Pediatric Allergy Clinic was started; to Dr. Lewis Webb Hill and Dr. Bret Ratner whose round tables and seminars in pediatric allergy under the auspices of American Academy of Pediatrics have done so much to make the subject of allergy interesting to pediatricians and to such internist-allergists as the late Dr. Aaron Brown, and to Drs. Robert A. Cooke, M. Murray Peshkin, George Piness, Milton B. Cohen, and Matthew Walzer who, in various ways, have encouraged and supported my work. I should also like to acknowledge my great obligation to Drs. Marion B. Sulzberger and Rudolf L. Bear for their kindness in helping me with numerous problems which have arisen in the course of studying the various allergic skin diseases in children. Dr. George L. Engel was most helpful in criticizing the chapter on psychosomatics although our points of view do not necessarily coincide.

My thanks are also due to Mrs. Olga S. Nell, librarian of the Rochester Academy of Medicine for much help in tracking down references, and to Mr. Louis J. Moskowitz and Mr. Maurice Liberman who gave advice on many pharmacological problems. I would also be remiss if in these acknowledgments I failed to express my appreciation to Mr. Manuel D. Goldman, friend, neighbor and

attorney for many years whose kindly understanding and complete competence has saved so much time for these writings by lifting from my shoulders many non-medical burdens.

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Lastly, I should like to express my thanks to the exceedingly well-trained young pediatricians who have worked with me as fellows in pediatric allergy: Dr. Harold I. Lecks of Philadelphia; Dr. Sheldon C. Siegel of Los Angeles; Dr. Maximilian Berkowitz of Haifa, Israel; Dr. Bing C. Lee of Taiwan (Formosa); Dr. Joseph L. Aponte of San Juan, Puerto Rico; Dr. Mary S. Boyden, of Lawrence, Kansas, and Drs. Douglas E. Johnstone and Marilyn F. Smelzer, of Rochester, N.Y. Their skepticism and constant questioning has done much to help me keep my feet on the ground in the study of this challenging and exciting subject of allergy in children.

With these acknowledgments and the feeling that this work could have been better done by older and wiser men in this field, with all humility I turn this book over to those interested in allergy in children.

JEROME GLASER, M.D.

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CONTENTS

	<i>Page</i>
INTRODUCTION	vii
<i>Chapter</i>	
1. THE INCIDENCE AND PROGRESSION OF ALLERGIC SYNDROMES IN CHILDREN	3
2. GENERAL CHARACTERISTICS OF THE ALLERGIC CHILD	11
Growth and development of the allergic child	11
Intelligence of the allergic child	12
Food dislikes in allergic children	12
Intercurrent infection and allergic disease	14
The thyroid gland and allergy in children	15
Allergy in identical twins	16
3. HISTORY TAKING AND THE PHYSICAL EXAMINATION	19
Physical examination	25
Progress notes	26
4. SKIN TESTING	28
Intradermal testing	35
Passive transfer tests	39
Skin testing in the newborn infant	40
Ophthalmic testing	41
5. RECAPITULATION	44
6. ALLERGY IN EARLY LIFE	48
Pathological physiology of allergic disease	48
Intrauterine sensitization	49
Fetal hiccoughs	51
Urticaria	51
Erythema neonatorum	52
7. GASTROINTESTINAL ALLERGY	55
Abdominal pain as a minor symptom	56
Abdominal pain of a subacute, recurrent nature	57
Severe abdominal pain simulating a surgical condition ...	57
Roentgenographical evidence of gastrointestinal allergy ..	57
8. COLIC	60
9. PYLOROSPASM AND HYPERTROPHIC PYLORIC STENOSIS	67
10. CHRONIC ULCERATIVE COLITIS	70

11.	THE CELIAC SYNDROME	78
12.	GASTROINTESTINAL ALLERGY— <i>Continued</i>	82
	Cyclic vomiting	82
	Geographical tongue	83
	Other gastrointestinal allergic disorders	84
	Regional enteritis	87
13.	THE ECZEMATOID DERMATOSES	90
	The eczematoid dermatoses of infancy childhood	91
14.	ATOPIC DERMATITIS	93
	General characteristics of the child with atopic dermatitis	93
15.	ATOPIC DERMATITIS— <i>Continued</i>	97
	Chronic atopic dermatitis	98
	Atopic erythroderma	101
	Atopic dermatitis by contact	103
16.	IMPORTANCE OF INHALANT ALLERGENS IN ATOPIC DERMATITIS	105
17.	THE TREATMENT OF ATOPIC DERMATITIS	108
	General measures in the symptomatic treatment of atopic dermatitis	108
	Treatment of local infection	109
	The "use test"	110
	Bathing	111
	Tar baths	111
	Soap substitutes	112
18.	LOCAL TREATMENT OF ATOPIC DERMATITIS	114
	Wet dressings	115
	Application of wet dressings	115
	Subacute and chronic atopic dermatitis	117
	Tar	117
	White tars	119
	Lassar's paste	120
19.	THE TREATMENT OF ATOPIC DERMATITIS WITH CORTICOTROPIN (ACTH) AND CORTISONE	124
20.	COMPLICATIONS OF ATOPIC DERMATITIS	127
	Impetigo	127
	Eczema vaccinatum	128
	Eczema herpeticum—Kaposi's varicelliform eruption	129

	Other infections complicating eczema	131
	Miscellaneous complications of atopic dermatitis	133
	Respiratory and gastrointestinal	133
	Renal disease	133
	Pyrexia	134
	Phenylpyruvic oligophrenia	134
21.	SUDDEN DEATH IN ATOPIC DERMATITIS	137
22.	HOSPITAL MORBIDITY AND MORTALITY OF ATOPIC DERMATITIS	139
23.	SEBORRHEIC DERMATITIS	143
	Differential diagnosis	144
	Treatment of seborrheic dermatitis	150
24.	ERYTHRODERMIA DESQUAMATIVA	154
25.	CONTACT DERMATITIS	157
	Technic of patch testing	157
	Treatment of contact dermatitis	161
	Poison ivy (<i>Rhus toxicodendron</i>) dermatitis	162
26.	ECZEMATOID DERMATOSES OF BACTERIAL ORIGIN	165
	Infectious eczematoid dermatitis	166
27.	NUMMULAR ECZEMA—CIRCUMSCRIBED NEURODERMATITIS	169
	Nummular eczema	169
	Circumscribed neurodermatitis	171
28.	BRONCHIAL ASTHMA IN INFANTS AND CHILDREN	174
	Latent wheezing	178
	Fever in childhood asthma	179
	Early appearance of emphysema in infantile asthma	179
	Symptomatological differences between infantile and adult asthma	180
	Other diagnostic aids	180
	Response of the asthmatic attack to medication	180
	Nasal eosinophilia	181
29.	THE DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA	183
	Congenital laryngeal stridor	183
30.	THE DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA—Continued	188
	Asthmatic bronchitis	188
	Foreign body in a bronchus	190

	Foreign body in the esophagus	191
31.	THE DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA— <i>Continued</i>	195
	The azygos vein and fissure	195
	Generalized obstructive emphysema of infancy (brochio- litis or capillary bronchitis)	202
	Fibrocystic disease of the pancreas (mucoviscidosis)	204
	Dust bronchitis	205
	Congenital lobar emphysema	206
32.	THE DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA— <i>Continued</i>	209
	Thymic asthma	209
	Miscellaneous conditions	211
33.	THE DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA— <i>Continued</i>	213
	Cardiac asthma	213
	Congenital heart disease	214
	Sighing dyspnea	214
	Post-encephalitic hyperpnea	215
	Ayerza's disease	216
	Bronchotetany	217
	The allergic cough	218
34.	COMPLICATIONS OF BRONCHIAL ASTHMA	221
	Emphysema	221
	Atelectasis and massive collapse of the lungs	221
	Air in the extrapulmonary spaces	223
	Heart disease and asthma	224
	Tuberculosis and asthma	225
	Spontaneous fracture of the ribs	225
	Death from asthma	226
35.	THE RELATIONSHIP OF THE TONSILS AND ADENOIDS TO BRONCHIAL ASTHMA	228
	Recurrent lymphadenoid tissue in the nasopharynx	229
36.	SYMPTOMATIC TREATMENT OF BRONCHIAL ASTHMA	233
	Routine management of asthmatic attacks following acute upper respiratory infections	237

	Bed rest	237
	Cough mixtures	238
	Nose drops	239
	Steam inhalations	242
	Oral administration of ephedrine	243
	Aminophylline suppositories	243
	Inhalation of epinephrine aerosol 1/100	244
	Epinephrine 1/1000 by hypodermic injection	245
37.	STATUS ASTHMATICUS	249
	Aminophylline	250
	Other medications in status asthmaticus	252
	ACTH and cortisone in status asthmaticus	253
	Intramuscular administration of ACTH	255
	Oxygen in status asthmaticus	256
	Bronchoscopy in status asthmaticus	256
	Miscellaneous procedures in status asthmaticus	256
	Epinephrine poisoning	257
38.	MANAGEMENT OF THE CHILD WITH CHRONIC ASTHMA	260
	Environmental control	260
	Education	262
	Physiotherapy in bronchial asthma	263
	Conclusion	264
39.	THE TREATMENT OF ALLERGIC DISEASES WITH CORTICO- TROPIN (ACTH) AND CORTISONE	266
	Indications for hormone therapy	267
	General procedures	268
	Choice of drug to be used	268
	Adverse reactions to ACTH and cortisone	271
	Potassium in relationship to ACTH and cortisone therapy	272
	Eosinophilia in pediatrics	274
	The eosinophil depression test	275
40.	CORTICOTROPIN (ACTH) AND CORTISONE IN PREGNANCY ..	278
41.	POLLINOSIS (SEASONAL ALLERGIC RHINITIS; TREE POLLINO- SIS; ROSE FEVER; HAY FEVER)	280
	Symptomatology	281
	Indications for specific treatment	282
	Masked pollinosis	283

	Skin testing with pollen extracts	284
	Treatment by the injection of pollen extracts	285
	The symptomatic treatment of pollinosis	290
42.	LESS COMMON DISEASES DUE TO POLLEN	295
	Vulvo-vaginal pruritis	295
	Dermatitis due to pollen	296
	Urticaria due to pollen	296
	Miscellaneous conditions due to pollen	297
43.	RECURRENT UPPER RESPIRATORY DISORDERS OF ALLERGIC ORIGIN AND PERENNIAL ALLERGIC RHINITIS	299
44.	VARIOUS FORMS OF URTICARIA, ANGIOEDEMA, ERYTHEMA MULTIFORME AND ERYTHEMA NODOSUM	311
	Urticaria and angioedema	311
	Treatment of urticaria	313
	Papular urticaria (lichen urticaria papuloso)	314
	Urticaria factitia	315
	Urticaria pigmentosa	316
	Erythema multiforme	317
	Erythema nodosum	318
45.	ALLERGY TO DRUGS	321
	Penicillin	325
	Technic (Matheson)	327
	Significance of the Skin Test	327
	Insulin	329
46.	ALLERGY TO VACCINES	330
	Death following vaccine injections	330
	Reactions following antirabies prophylaxis	333
47.	THE ANTIHISTAMINES	335
	Dosage of the Antihistamine Drugs	335
	Toxic Reactions to the Antihistamines	336
	Treatment of antihistamine intoxication in childhood	337
48.	PREVENTION OF ALLERGIC REACTIONS TO DRUGS	339
	Local anesthetics	340
49.	ANAPHYLACTOID PURPURA (Schönlein-Henoch Syndrome) . .	342
	Treatment of the Schönlein-Henoch Syndrome	348

50.	NEUROALLERGY IN CHILDHOOD	350
	Neurological complications of antirabies prophylaxis	352
	Meningitic serum reactions	352
	Electroencephalography in allergic children	354
	Epilepsy	356
51.	MIGRAINE	360
	Symptomatic treatment of migraine	366
52.	ALLERGY TO INSECT BITES AND STINGS	369
53.	OCULAR ALLERGY	376
	Vernal conjunctivitis (vernal catarrh)	376
54.	PHYSICAL ALLERGY	380
	Treatment of allergy to cold	385
55.	EOSINOPHILIC PNEUMONOPATHY (LÖFFLER'S SYNDROME; TROPICAL EOSINOPHILIA)	387
	Löffler's syndrome	387
	Tropical eosinophilia	389
56.	THE ALLERGIC TENSION-FATIGUE SYNDROME	392
57.	MISCELLANEOUS CONDITIONS OF INTEREST TO THE PEDI- ATRIC ALLERGIST	396
	Favism	396
	Allergic arthritis	398
	Transient synovitis of the hip joint	399
	Genitourinary allergy	400
	Enuresis of allergic origin	401
	Allergic parotitis	402
	Aphthous (ulcerative) stomatitis	402
	Bronchiectasis	404
	Kartagener's syndrome	406
	Isolated myocarditis	408
	409
58.	THE COLLAGEN DISEASES	409
	Rheumatic fever	410
	Rheumatoid arthritis	411
	Polyarteritis (periarteritis nodosa)	414
	Lupus erythematosus	417
	Progressive systemic sclerosis (generalized scleroderma) ..	420
	Dermatomyositis	422

59.	PSYCHOSOMATIC ASPECTS OF ALLERGIC DISEASE IN INFANCY AND CHILDHOOD	425
60.	DIETARY TREATMENT OF ALLERGIC DISEASE	436
	Preliminary considerations	436
	Hypersensitivity to human breast milk	436
	Transmissions of food proteins through breast milk	438
	Inherited sensitivity	439
	Sensitivity to osmyls	439
	Sensitivity as a result of biogenetic relationships	439
	Transmission of injected pollen extract through the breast milk	440
	Transmission of drugs through the breast milk	440
	Transmission of foreign proteins through cow's milk	441
61.	COW'S MILK—GENERAL CONSIDERATIONS	444
	Severe idiosyncrasy to cow's milk	446
	Cow's milk sensitivity in a lower animal	448
	Galactosemia	449
62.	SUBSTITUTES FOR COW'S MILK IN INFANT FEEDING	452
	Soybean milk	453
	Goat's milk	457
	Other animal milks	458
	Meat base milks	459
63.	THE ELIMINATION DIET	463
	Vitamins in the elimination diet	466
	Vitamin C	468
	Unsaturated fatty acids and atopic dermatitis	469
	Management of the elimination diet	470
	The rotary diversified diet	471
64.	CLIMATE AND ALTITUDE	475
	The relationship of altitude to allergic manifestations	479
65.	THE ALLERGIC CHILD IN CAMP	483
66.	ROUTINE PROPHYLAXIS IN ALLERGIC CHILDREN	489
67.	THE PROPHYLAXIS OF ALLERGIC DISEASE	493
68.	ADDENDA	509
	INDEX	519

ALLERGY IN CHILDHOOD

CHAPTER 1

THE INCIDENCE AND PROGRESSION OF ALLERGIC SYNDROMES IN CHILDREN

THE INCIDENCE of major allergic diseases (typical, marked asthma, pollinosis, chronic or recurrent urticaria, and recurrent gastrointestinal disturbances with one of the foregoing although not necessarily of severe degree) is generally accepted as about 10 per cent of the population (6). Surveys have never been made for children alone, but Cohen (2) stated that, among many children studied at Western Reserve University and pronounced normal by their physicians, about 50 per cent eventually developed some evidence of allergy. The only published observations on the incidence of allergy in a general pediatric practice are those of London (3) who, in 1937, among 1500 children found allergic disease in ninety-nine, or 6.6 per cent. It is my impression that the incidence of major allergic disease in such a practice is considerably larger, but there are no statistics other than London's whose findings are much to the contrary.*

Clein (1) on the west coast and of Ratner *et al.* (5) on the east coast, examined the incidence and progression of allergic syndromes in children. MacKinney and Glaser (4), in attempting to extend and amplify this problem, studied the course of 516 successive patients from my office files. The only criterion of selection was that the record be that of an allergic child not over ten years of age at the time first seen. The records of 200 successive adults, seen in consultation, were used as a basis for comparison. For the past ten years this

* In a personal communication Dr. London stated that in a similar as yet unpublished study in 1951-52 the incidence of allergic manifestations (new patients) was 6 per cent, just about the same as in the previous study. Dr. London commented that these figures are surprising because it was felt that the incidence of allergic disease was on the increase and that perhaps this impression is based on the fact that with a large backlog of patients the allergic children stand out because they are seen more often than other children without allergic manifestation.

practice, as concerns new patients other than consultations, has been limited to allergic children or newborn infants whose parents or siblings are allergic, and the files contain a disproportionate number of severe and persistent problems as compared with the pediatrician's customary practice.

Tables I and II compare our figures of the incidence of various allergic syndromes with those in the earlier series of Ratner and

TABLE I
COMPARATIVE INCIDENCE OF ALLERGIES

<i>Syndrome</i>	<i>J.G. 516 Cases</i>	<i>Clein 100 Cases</i>	<i>Ratner 250 Cases</i>	<i>J.G. 200 Adults</i>	<i>Ratner 315 Adults</i>
Colic	21.7 %	23.0%			
Eczemas		33.0%	44.4%		11.0%
Atopic	38.6 %			1.7 %	
S.D.	7.37%			3.83%	
P.A.R.	28.2 %	59.0%		35.0 %	
R.U.R.I.	30.9 %			9.6 %	
Pollinosis	33.0 %	38.0%	10.4%	41.6 %	28.0%
Asthma	53.4 %	26.0%	63.2%	41.6 %	53.0%

TABLE II
COMPARATIVE INCIDENCE OF ALLERGIES

<i>Syndrome</i>	<i>J.G. 516 Cases</i>	<i>Clein 100 Cases</i>	<i>Ratner 250 Cases</i>	<i>J.G. 200 Adults</i>	<i>Ratner 315 Adults</i>
Urticaria	16.3 %	12.0%	10.4%	35.0 %	8.7%
Migraine	1.16%	2.0%		10.96%	
G.I.	2.9 %	20.0%		2.38%	
Drug Reactions	5.24%			10.5 %	
Contact dermatitis	1.55%			12.9 %	
Conjunctivitis	0.97%			2.38%	
Sensitivity to insect bites	1.16%				

Clein. The inclusion of colic in Table I does not mean that we consider it to be always or even commonly an allergic disease. However, we have the impression that colicky babies, more frequently than the others, go on to develop subsequent allergies even when it cannot be proved that the colic is of allergic origin. The incidence of "eczema" in the three studies is quite similar. I feel that a clinical differentiation between atopic and seborrheic dermatitis is practical in many instances and that it has prognostic significance. Eighty per

cent of infants with atopic dermatitis progressed to other allergic syndromes whereas this occurred in only 25 per cent of the patients with seborrhea.

I also believe that perennial allergic rhinitis (hereafter referred to as PAR) and recurrent upper respiratory infections (hereafter referred to as RURI) are distinguishable syndromes in children. Taken together they match Clein's figures for PAR.

The pollinosis figures in upper New York State and the Pacific Northwest are quite similar despite the absence of ragweed in the latter. In Ratner's series collected about New York City the incidence of pollinosis seems lower. It is interesting to note that despite similar amounts of eczema and upper respiratory allergies there is only half as much asthma in the Pacific Northwest as in the Northeast. The two adult series confirm the general impression that eczema and RURI are less common in adults whereas pollinosis and PAR are more common. Of less common knowledge is the fact that asthma is more common in allergic children than allergic adults. Table II indicates that urticaria and minor allergic syndromes are more frequently encountered in adult allergic patients.

Figures 1, 2, and 3 show the incidence of onset of five major allergic syndromes at various years in childhood. The heavy line at the top indicates the actual number of patients in the series that reached any particular age before or during our observation. The height of any column indicates the per cent of the number of patients who developed that particular allergy at that particular age. This gives a closer approximation to the true incidence of these allergic syndromes than a simple charting of the number of cases. Thirty per cent of our patients gave a history of, or were observed to have, eczema at 3 months of age. New cases of eczema continue to occur in considerable numbers through the first two years of life; then in a lesser degree through the sixth year after which no new cases occurred. Forty-three per cent of our total of 276 cases of asthma commenced during the first two years of life and 87 per cent before the seventh year. Similarly, pollinosis begins increasing in incidence at eighteen months, 72 per cent of the cases beginning before seven years. RURI and PAR are less dramatic and tend to parallel one another. The peak of onset for all the major syndromes

INCIDENCE OF ONSET OF MAJOR ALLERGIES

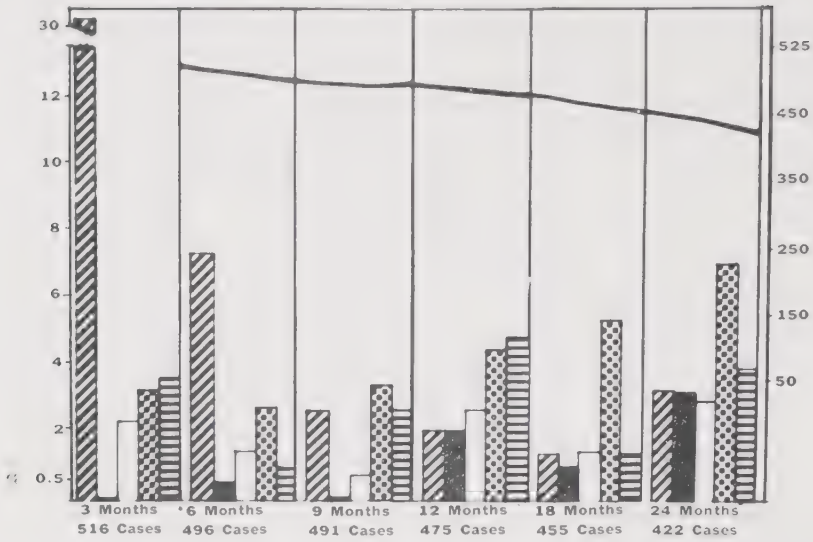


FIG. 1

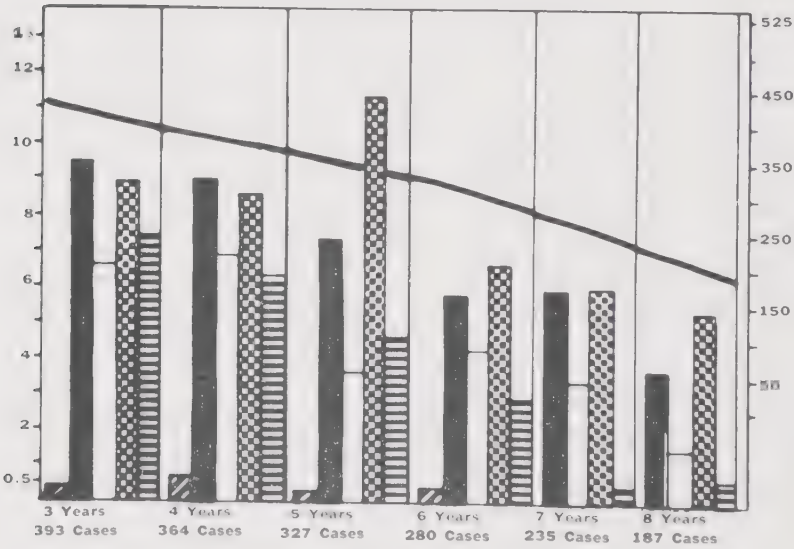


FIG. 2



except eczema seems to be the third, fourth and fifth years of life.

Many allergists feel that, once the allergic diathesis has been established, additional allergies are more likely to follow. Multiple allergies occurred in 79 per cent of our 516 cases. It is our impression that patients with atopic dermatitis are more prone to develop

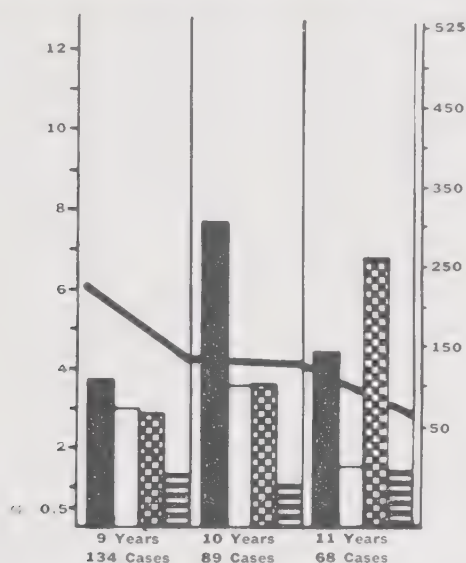


FIG. 3

additional major allergic syndromes than any other. Ratner found that 59 per cent of his children having "eczema" eventually developed upper respiratory allergies and asthma; our figure of 80 per cent for atopic dermatitis is even higher. Table III shows the progression of 172 cases of atopic dermatitis to upper respiratory allergies or asthma. Atopic dermatitis progressed to eventual asthma in ninety-one instances (53 per cent), in thirty-eight cases without any other intervening syndromes. In fifty-three cases other respiratory allergies (RURIs, PAR or pollinosis) preceded or occurred simultaneously with the onset of asthma. Eighty-one cases of atopic dermatitis did not develop asthma although the majority of them did develop upper respiratory allergies. Only thirty-four cases (20 per cent) remained arrested at that stage of allergy. Table IV shows the progression of upper respiratory allergy to asthma when unaccompanied by the presence or history of eczema. Fifty (42 per cent) out of 119 cases of single or multiple upper respiratory allergies

TABLE III

PROGRESSION OF ATOPIC DERMATITIS TO UPPER RESPIRATORY ALLERGIES OR ASTHMA

1. Eczema with asthma	91 cases	
Eczema→asthma, only	22 cases	42%
Eczema→asthma→R.A.	16 cases	
		Asthma→resp. allergies
Eczema ↗	53 cases	
↘ Resp. allergies→asthma		
2. Eczema without asthma	81 cases	
Eczema→R.A.→no asthma	34 cases	
R.A.→eczema→R.A.	13 cases	
Eczema→no sequellae	34 cases	

went on to eventual asthma, sixty-nine did not. Atopic dermatitis is more likely to be followed by further major allergic disease than any other major allergic syndrome. In addition, asthma follows atopic dermatitis as frequently, if not more frequently, than it follows upper respiratory allergies. Asthma occurred suddenly, without previous manifestations of any allergic tendency, in 93 of the 276 cases (34 per cent) indicated in Table V. This happened at any pediatric age (3 wk. to 14 yr.), with the majority of such cases beginning before two and one-half years of age. In thirty-four instances, other syndromes occurred simultaneously, predominantly RURI.

The above observations indicate that once the allergic diathesis is established, additional allergic syndromes are very likely to follow, especially if eczema has occurred. The great bulk of allergic syndromes has become established by the sixth year of life. There is no set pattern of this progression. The paramount importance of allergic "prophylaxis" and treatment in the pediatric age group is obvious.

TABLE IV

UPPER RESPIRATORY ALLERGIES WITHOUT ANTECEDENT OR PRESENT ECZEMA
(*Perennial allergic rhinitis or recurrent upper respiratory infections*)

Progressing into asthma	50
No sequellae	69
Single upper respiratory allergies	44
Multiple upper respiratory allergies	25

TABLE V
OCCURRENCE OF ASTHMA WITHOUT PRECEDING ALLERGIC DISEASE

Total case incidence of bronchial asthma	276
Onset without preceding allergic disease	93 (34%)
Mean age of onset	2.6 yr.
Range	3 weeks to 14 yr.
Simultaneously occurring syndromes (34 patients):	
RURI	23
PAR	14
Pollinosis	10
Atopic dermatitis	3

These studies may perhaps shed some light as to why the absolute incidence of allergic disease in this country has, as is generally believed, steadily increased for many years. If this is actually the case, altho there is no statistical evidence to confirm or deny this impression, there is probably more than one factor involved. One of the more obvious is the wide distribution of the ragweed plant and the ease with which ragweed pollinosis appears to be acquired. Since ragweed is a parasite of cultivated soil, as the population grows, more and more land comes under cultivation and more ragweed grows and as a result the number who suffer from ragweed pollinosis and its complications may be expected to increase. With the increased use of the automobile for long distance driving thru the summer the exposure of a large segment of our population to terrific doses of pollen as compared with the old horse and buggy days is still another reason for an absolute increase in the incidence of pollinosis.

There is, however, another possible explanation for an absolute increase in the incidence of allergic disease. The studies of Grulee and Sanford (2a) have shown that seven times as many bottle fed (cow's milk) babies develop eczema as breast fed (human milk) infants. These findings, together with those just discussed which indicate that 80 per cent of infants with eczema (atopic dermatitis) subsequently develop respiratory allergic disease in conjunction with the fact that breast feeding in this country has been largely abandoned during the past twenty-five years, serve as a very adequate explanation for the absolute increase in allergic disease, if such an increase has actually taken place. If this is true the proponents of breast feeding are provided with a very potent argument.

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Chapter 2

GENERAL CHARACTERISTICS OF THE ALLERGIC CHILD

KUGELMASS (9) stated that a rather constant concomitant of latent allergy in infants is retro-auricular intertrigo. The typical lesion is an erythematous linear area with a glazed appearance. This is most pronounced beneath the lobes of the ears and if the ear is pulled forward a fine, striated area exuding thin serum appears. There is no scaling as a rule, but it does occur. Kugelmass states that Sabaroud has shown that this condition is due to a non-hemolytic streptococcus.

I have observed this sign in infancy, but believe that it is more commonly associated with seborrheic dermatitis, which is certainly not an allergic disease, than with atopic dermatitis. However, since seborrheic dermatitis in infancy may pass by almost imperceptible degrees into atopic dermatitis, this sign is perhaps worthy of some consideration. Kugelmass also states that a hairless, scaly scalp or a desquamated dry scalp is a helpful but an inconstant sign for determining allergy in the newborn. The significance of this observation needs further study. Campbell (3) stated that a history of excessive perspiration is frequently obtained in allergic children. While this might be expected in view of the greater vasomotor instability of allergic children, I have not been particularly impressed by it. Even in normal children excessive perspiration is not unusual, probably being related to immaturity of the vasomotor system.

GROWTH AND DEVELOPMENT OF THE ALLERGIC CHILD

Cohen and Abram (6) studied the growth pattern of allergic children by means of the Wetzell grid which they felt, afforded a simple, inexpensive and reliable method of following growth and detecting early growth failure. Five hundred and three observations were made on 150 allergic children seen in private practice and

compared with 622 observations on 102 non-allergic controls. The conclusions were drawn that allergy occurs more frequently in children, especially boys, who are constitutionally slender. They found active allergy to be a common cause of growth failure. When the allergy was controlled, there was a corresponding growth repair provided the diet was adequate.

Welsh (18), also using the Wetzell grid as an index, followed the growth records of thirty-four allergic children for periods of twelve to one hundred months. Apparently most or all of these children had respiratory symptoms. All were under attempted allergic control during the time studied and only two of the thirty-four children showed signs of growth failure.

INTELLIGENCE OF THE ALLERGIC CHILD

Balyeat (1), in 1929, studied the general health and mental activity of eighty allergic and eighty non-allergic children. As a result of this study he concluded that most allergic children are above normal in general health and that their mental activity is far above normal.

Piness *et al.* (11), in 1936, made a much more detailed survey. They studied 145 children attending the allergy clinic of the Los Angeles Children's Hospital. The children ranged in age from five and one-half to fifteen and one-half years, the average age being nine years. This group was compared with a similar group of unselected children in Los Angeles schools. They found that the allergic children were very similar in intellectual level to a normal group, with the variations of a normal group. They included children of superior, average, normal, and inferior intelligence. As far as school success, the allergy group was similar in grade placement to the normal group. However, the illness and the discomfort from the allergic diseases did not seem to hamper the children in school in as great a degree that might be expected from other forms of illness. Chobot *et al.* (4) in their studies of the mental activity of allergic children also found that they gave no evidence of special proficiency or deficiency in any field covered by standard mental tests.

FOOD DISLIKES IN ALLERGIC CHILDREN

The problem of food dislikes is very complicated and involves many psychological factors. Whether one likes or dislikes a food de-

pendes a great deal upon what one has been accustomed to and the associations which arise in conjunction with the taste, color, odor, and consistency of any particular food. In the case of allergic individuals, it is often thought that food dislikes represent distinctive defense reactions against harmful foods. Vaughn and Pipes (17), in an effort to decide this question, studied a group of 500 individuals (ages not stated). They found that approximately 80 per cent, allergic or non-allergic, have one or several food dislikes. Of approximately 20 per cent of allergic individuals expressing food dislikes, at least one food so mentioned was found to be allergenic. Among 80 per cent of allergic individuals there was found no correspondence between dislikes and foods causing allergy. While food dislikes may be responsible for food allergy, this, according to Vaughn and Pipes, is not the rule and foods disliked cannot be relied upon as indicative of allergic sensitization.

Dr. B. Z. Rappaport, in discussing this presentation, stated that, if one could obtain a careful history of food likes and dislikes in children under three or four years, different conclusions might be drawn from those expressed by Vaughn and Pipes. I am inclined to agree with Dr. Rappaport.

Vaughn and Pipes stated that the one outstanding exception to food dislikes causing allergic reactions occurs in those cases in which gastrointestinal symptoms follow the ingestion of the allergic food after such a short interval that the patient has himself recognized the cause and effect relationship. They found that the most common food to do this, in both children and adults, is egg. Williams (20) studied a group of 150 school children who refused or showed a disinclination to take milk in school. Fifty-eight and seven-tenths per cent refused because its ingestion was always followed by allergic manifestations of some sort. Almost without exception symptoms were gastrointestinal. Of the eighty-eight children, nausea was the complaint among forty-seven, vomiting in thirty-seven, and severe abdominal pain in one. The only two who did not have gastrointestinal symptoms had asthma and eczema. Among those who reacted with vomiting, fourteen had migraine. Twenty-four per cent of the total number disliked milk but had no symptoms from it. Williams found a personal or family allergic history in all except four of this group, and concluded from this that aversion to milk may be subconsciously protective. However, so many families have

a history of allergy that such conclusions, according to Vaughn and Black (16), are questionable. The remainder of the children gave reasons not connected with possible allergy.

INTERCURRENT INFECTION AND ALLERGIC DISEASE

The temporary clearing of intractable allergic symptoms which occasionally occurs following an acute intercurrent infection, particularly when accompanied by fever, is a well known phenomenon. This does not, however, always occur and Feingold (7) found that in general an acute infection in an allergic child produced one of two patterns. The first was observed in association with pertussis and the viral infections, including measles, chicken pox, mumps, generalized vaccinia, and epidemic virus infections. This group of diseases usually confers an active immunity after a single attack and their blood picture is a leucopenia with the exception of pertussis which evokes a lymphocytosis. In this group there is generally clearing, at least temporarily, of the allergic manifestation.

The second pattern is observed in association with upper respiratory infections accompanied by a polymorphonuclear leucocytosis and these conditions confer little or no immunity and the clinical allergic manifestations, particularly bronchial asthma, may be aggravated.

The extension of observations of this nature may help clarify the interrelationship between infection and allergy and reveal data explaining the underlying mechanisms.

Fries and Borne (8), in 1953, reviewed the literature of this subject and studied sixteen children, eleven with measles, two pneumonia, one scarlet fever, and two upper respiratory symptoms with sore throat, and a series of sixteen children suffering from generalized vaccinia whose course was followed only during the hospital stay for the acute illness. All of these patients had suffered severely with asthma, perennial allergic rhinitis and chronic atopic dermatitis. Relief of the allergic symptoms usually occurred at the height of the fever and continued for a period of five days to one year, the majority for a few weeks. All but one eventually relapsed. The exception was a one-year-old child with the celiac syndrome believed to be of allergic origin and followed for a period of five years after the febrile episode. It is the fever associated with the infection which appears to be the beneficial agent. If two allergic states coexist, both

appear to be similarly benefited. Fries and Borne felt that improvement with acute infection, when it occurs, may lie in a mobilization of the endocrine defense mechanisms during fever or possibly in increased histaminolytic activity. There is, however, unfortunately no constant beneficial effect of fever or intercurrent infection on the allergic state. Further reference to this subject is made in Chapters 14 and 17.

THE THYROID GLAND AND ALLERGY IN CHILDREN

Topper and Mulier (15) and Lesné *et al.* (10) were among the first to report on the basal metabolic rate of allergic children. Topper, in twenty-four cases of asthma, found the B.M.R. within normal limits between attacks but on the lower side. Lesné *et al.* reported the same findings and also observed that this occurred in urticaria and angio-neurotic edema in children. Chobot and Dundy (5) stated that elevation of the blood cholesterol is an unreliable guide for the administration of thyroid in allergic children and found thyroid therapy to be of no particular value. Quarles van Ufford (12), in studying the basal metabolism of allergic individuals, noted that an increased rate occurred more commonly than a decreased rate, and that decreased rates occurred predominantly in children. He noted that thyroid therapy improved the general condition of these patients but had little effect upon the asthma.

More recently, the whole subject of hypothyroidism in pediatric allergy has been discussed by Reilly (14). He pointed out that response of the end-organ (target tissues) is significant. Hypothyroidism can affect all parts of the body but at a given time not all tissues seem to be deficient or react equally to a given lack. Some tissues, which seem to be doing normally on a reduced ration of thyroid substance, will show deficiency later. This may well be due to a decreased sensitivity of the end-organs, resulting from a variety of factors, particularly infection, growth stresses and possibly allergic states. In general, hypothyroidism does not occur any more frequently in the allergic state than in the whole childhood population. The indication for thyroid substance would therefore be the same, i.e., the presence of hypothyroidism. However, thyroid substance has some non-specific systemic effects; it is calorogenic, sympathicotonic, dehydrating, and appetite stimulating. All these actions appear at times in the allergic patient receiving thyroid sub-

stance. Many chronic diseases, especially if severe enough, in childhood are accompanied by failure to grow well in height, weight and other usual measurements of physical development. Allergic states of long duration and great degree can cause such a failure of proper growth and development. Examination of some such children reveals a low basal metabolic rate, definite retardation of epiphyseal development and other evidences pointing to endocrine and particularly thyroid deficiency. Some of these malnourished and physically retarded children have been known to respond to thyroid substance. This may be particularly true of the chronic malnourished asthmatic or eczematous child. This is not *prima facie* evidence that the child has hypothyroidism. The chronic degree of the allergic condition, and accompanying malnutrition, might well suppress activities in the endocrine glands and in the thyroid particularly. Very likely in such states the thyroid substance may exert a sympathicotonic effect. The dehydrating action that can occasionally be induced with thyroid substance when treating overweight, eczematous infants may also be helpful. These effects should, however, be called symptomatic therapy.

Ratner (13) has recommended studies of the nail fold capillaries and also the centers of ossification of the wrists such as may be made in the routine fluoroscopy of the allergic child during the course of the physical examination as aids for the rapid and direct appraisal of hypothyroidism. He pointed out, however, that retardation in epiphyseal development and a typical capillary picture may not be due to lack of thyroid hormone alone. While I have had no experience with capillary microscopy, I have found that evaluating the bone age by means of fluoroscopy of the wrists is rather difficult because of the wide normal variations. However, where the bone age is greatly below normal (say over two years) the administration of thyroid as well as the correction of anemia and dietary and vitamin deficiencies, while having no specific effect upon the allergic condition, may, nevertheless, contribute to the improved health of the child.

ALLERGY IN IDENTICAL TWINS

Bowen (2) has briefly reviewed the literature concerning allergy in identical (monozygotic) twins and reported his own observations

of fifty-nine pairs. Twinning occurs in about one out of every ninety normal births and only one set of twins out of every four or five is monozygotic. Contrary to other observers, Bowen found co-existing allergy in twins to be the exception rather than the rule. Only seven sets out of the fifty-nine presented allergies in both twins and in this the sex distribution was about equal. The seven pairs represented three pairs with juvenile eczema who later developed bronchial asthma and two other sets had bronchial asthma with nasal allergy. The remaining fifty-two pairs had bronchial asthma with coexisting nasal obstruction in some patients. In this group only one was affected in each set of twins to such a degree that medical help was sought.* Usually when one twin developed an upper respiratory infection, the same condition occurred in the other twin but the non-allergic twin would not have an attack of asthma as did the allergic twin. Bowen remarked that the non-allergic twin was usually the more dominant, assuming a certain leadership. In over 85 per cent of Bowen's twins there was a familial incidence of allergy.

Bowen pointed out that many of these children first experienced their symptoms as early as two months, which poses an interesting question for the proponents of maternal rejection. Bowen feels that his study also challenges the concept that certain maternal dietary restrictions during pregnancy may make allergy less likely to appear in the newborn and also the concept that allergic manifestations are the result of placental transference, for if this were true he feels that he should have had fifty-nine cases of bilateral allergy and not seven, as actually occurred. The impression gained from my personal experience confirms Bowen's findings. However, these are so important and so at variance with generally accepted beliefs that further exploration of this field by other investigators is much to be desired.

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HISTORY TAKING AND THE PHYSICAL EXAMINATION

THE EXAMINATION made by a specialist consists of three principal parts: 1) the history; 2) the physical examination, and 3) the special tests pertinent to the specialty. In allergy, and this is true both for children and adults, the most important of these is the history. Details of history taking, with particular reference to adults, have been thoroughly discussed by Rackemann (3) and by Swineford and Weaver (8). For children it is my custom to take a detailed history and make a complete physical examination at the time of the first visit. This must be done with great care, and if the child presents a difficult problem, such as chronic asthma or atopic dermatitis, may require an hour to an hour and a half. It is always requested that someone accompany the parent and child to the office so that the parent may be interrogated alone while the child, supervised by the parent's companion, is amusing himself in the waiting room which is particularly designed for that purpose. In many instances it is practically impossible to take an accurate history with the child in the same room, as the presence of the child distracts both the parents and the physician. The parent, for purposes of this discussion, refers to the mother, since the father, as in most history taking in pediatric practice, usually is unfamiliar with the pertinent facts.

While a blank piece of paper, a pen and plenty of time are said by some to be the ideal prerequisites for history taking, I prefer to use history forms. Unless this is done, many pertinent questions may not be asked and much valuable information thereby lost.

After the customary pediatric history is taken, I employ the form shown in Tables VI and VII for the purpose of taking the allergic history. This is a very simple outline which has been found highly practical. Most of it is self-explanatory. The physician using such a form can very easily add various items depending upon his per-

sonal preferences. For example, in early infancy, I commonly insert a note under the line starting with "PAST HISTORY" as to whether or not the mother had any particular food cravings resulting in overindulgence in those foods during pregnancy. This is indicated simply by inserting the one word, "Pica." If she had no pica the symbol O is inserted after this word; if she had, the foods are noted here. The significance of this will be noted shortly. Many other similar variations are possible in a form of this type.

For the purpose of recording the progress of the child, Schwartz (6) employs a simple ten-year chart blocked in squares, the abscissa

TABLE VI

Allergy Record		Hist. No.	
Address:		Ref.	
Date: ; Age		Tel.	
Occupation		M S W D	
CLINICAL DIAGNOSIS:		Parent	
(1)	.	(4)	.
(2)	.	(5)	.
(3)	.	(6)	.
CHIEF COMPLAINTS:	Onset	Month	Place
PAST HISTORY: Colic as infant		Vomiting as infant	
Group	Eczema		
Pollinosis	Skin rash		
Migraine	Asthma		
Cough or colds	A E or Urticaria		
P.A.R.	Other manifest.		
OPERATIONS: T & A	TETANUS TOXOID		
	Booster tetanus		

of which indicates the month and the ordinate the year. The squares are filled in with various symbols which indicate the type of allergic manifestation. Such a record will show at a glance in what month the child's symptoms appear, the frequency of attacks, what systems are involved, and any change of the shock organ bearing the brunt of the allergic attack. Such a record facilitates, also, the evaluation of therapy. I have not personally used it but other pediatric allergists have found it very helpful.

It is a good plan to allow the mother to talk for a few minutes regarding the things which are uppermost in her mind before questioning her specifically. This allows one to get a general idea of the problem if this was not sufficiently obtained while taking the routine

TABLE VII

FAMILY HISTORY:

<u>EFFECT OF:</u>		Heat	Cold	Diurnal variation	Change of Weather
Seasonal variation					
Dampness				Fatigue	
Exercise				Dusting	
Nervousness				Contact disagreements	
Known food disagreements					
Food dislikes				Hobbies	
Food likes					
Pillow				Mattress	
Animals				Rug pads: Ozite	Others
Plants				Oriental rugs	
Furs					
Cosmetics					
<u>TEETH</u>				B.M.R.	
New clothing					
New Furniture					
Has been living in same dwelling					
Bowel movements					
Menses					

DRUG DISAGREEMENTS

Previous skin tests by Dr.	Date
Indicated sensitivity to	
Previous treatment	

pediatric history. Then, one may proceed to specific questioning. The discussion of the chief complaints is in no way different from that employed for adults. It is very important to try to associate significant events in the history with exact dates. When the mother's memory is vague, she is asked, respectively, concerning the season of the year and then the month and then, if possible, the day of the month and the circumstances associated with any specific occurrence. In time, as the progress notes on the patient's record are made, the recurrence of certain events at particular times of the year, or under the same set of circumstances, may develop significant meaning. The "colds" recurring yearly the first week in September about the time school opens may be the first sign of ragweed pollinosis; asthmatic attacks occurring only or most frequently when visiting the grandparents may result from exposure to environmental factors, such as pets. Special articles of clothing, bedding or furniture may be associated with attacks. A child sufficiently sensitive to goat dander may have an attack of asthma after playing or sleeping on a

mohair couch. One of my most difficult problems was solved after I discovered that a most severe attack of asthma occurred when this girl put on a silk bathrobe after she had been confined to bed for a minor illness. In another instance, a girl's scalp began to itch when she put on a hat with a silk lining.

In the discussion of the past history there are some essential points of difference between the adult and the infant or child. The allergist should know, for example, whether the mother had any particular food cravings during pregnancy, as occasionally overindulgence in any one particular article of food may possibly sensitize the infant to that food. Such incidents, described by Ratner (4, 5), though rare, are interesting and illuminate the problem of allergy in childhood. It should be a routine measure to warn the mother of a potentially allergic child (i.e., a child one or more of whose parents or siblings is allergic) to eat a wide variety of food during pregnancy and not concentrate, as pregnant women occasionally do, on any particular single item.

Whether or not sensitivity to human breast milk actually occurs is problematical. Whether or not the child is breast fed, however, is a matter of importance because almost any food or drug may pass through with the breast milk in sufficient concentration to cause allergic manifestations in the infant. These factors are considered under the discussion of breast milk. A leading question is, "Did you have any trouble finding a formula suitable for the child?" Any infant who has had repeated changes in formulae because of gastrointestinal discomfort, vomiting, diarrhea, or failure to gain properly is commonly an allergic infant.

To continue with the discussion of the form history with reference to Table VI, little help is obtained from a history of croup. No thorough studies of the relationship of simple, spasmodic croup to allergy have yet been published, and I feel that croup is of little importance with respect to allergic disease. The number of "colds" a child has is important because the child who has "one cold after another" commonly has nasal allergy. PAR refers to perennial allergic rhinitis, and here the complaint is that the child "won't blow his nose," or breathes with his mouth open, or has a nasal voice. AE refers to angioedema. The age at which the tonsils and adenoids were removed is important. Our preliminary studies sug-

gest that practically every child who has to have this operation before the age of three years, and any individual who has to have this operation more than once, is commonly allergic. The time of the year at which the operation is done is also important. Asthma will very frequently follow adenotonsillectomy in children with pollinosis if the operation is done during the pollen season.

Because allergic children are more likely than others to develop sensitivity to horse serum or, if sensitive, to react unpredictably to injection of horse serum, one should always inquire as to whether or not the patient has had tetanus toxoid. If not, it should be most strongly recommended. Bovine tetanus antitoxin (manufactured by Sharpe and Dohme) is again on the market and one should remember this for patients not immunized against tetanus and sensitive to horse serum (1). It should not be used, however, in milk or beef sensitive individuals.

The family history is of little importance except as contributing evidence when the diagnosis of allergy is in doubt. Generally speaking, we find more allergic disease in families with preexisting allergy than in families where such allergy does not exist. In pediatrics one is somewhat handicapped because occasionally allergic manifestations in the parent may not develop until years after allergy has occurred in one of their children.

Seasonal and diurnal variations of allergies are of some importance. Allergies which occur in summer may be related to pollen. Occasionally one may see very bizarre manifestations of pollinosis, as, for example, vaginitis in young girls. This subject will be discussed more thoroughly in subsequent chapters. Individuals with allergic rhinitis due to house dust, feathers or bedding are likely to have an increase of symptoms on arising in the morning when the change in air currents through the nose upon awakening may stimulate a reaction. Many respiratory allergies are made worse by change of temperature and by dampness. It is quite possible that these factors produce important reflex reactions in the nervous system but this subject is almost completely unexplored.

Clinical sensitivity to house dust is common. It is always best, in asking about this and similar suspected sensitivities to say, "Mother, suppose you had never in your life seen a doctor, could you say that house dust, in any way, causes your child to have trouble?" Other-

wise, the mother is likely to reply that house dust does bother the child, and when you ask how this is known she will state that at one time he was tested with house dust and reacted to it. This, of course, does not mean clinical sensitivity. One endeavors to determine from the history whether or not there is *clinical sensitivity* to specific allergens such as house dust, foods, animal pets, etc., because this is more important than the results obtained by skin testing. If a mother knows that house dust or dog dander causes her child to wheeze it doesn't matter what the results of skin tests with those allergens are. Even if negative these allergens must be given every consideration.

In questioning regarding contacts, the question is best phrased, "Mother, is there anything, such as soap, silk, wool, poison ivy, or anything else, which irritates your child's skin unduly on contact?" A suspected food sensitivity requires a review of the child's dietary regimen. Useful questions are: "What foods does your child dislike that most children like?"; "What does he like especially well?," and sometimes leading questions, such as, "What happened the first time he ate egg?" and "How much milk does he drink a day?" In the case of multiple food sensitivities, it is my custom to give the mother a list of foods to check (see Table VIII). She is to circle the foods which she knows, by experience, disagree with the child; place an "X" before any foods she suspects; underline all foods eaten as often as once a week, and put a check before foods eaten less often. If the mother takes the list home, studies it carefully and returns it, the physician will have some valuable information for guidance on necessary skin tests and subsequent dietary instructions.

One can often inject a little propaganda into the history taking. For example, when one asks whether the child sleeps on a pillow, the parent can be advised, if the child does not yet have one, that the best pillow she can buy for him is one of sponge rubber or a suitable plastic. Also, if a mattress is needed, one of similar material is preferable. In the same way, when asking about animal pets, if the family has none, one may say that since the child is allergic he will be much better off if no animal pets with fur or feathers are ever acquired. If such pets are present, the parents should be instructed (regardless of the results of subsequent skin tests) that in event the animals die they should not be replaced. When asking about ozite

floor pads, or other felt pads which are made of hog and cattle hair, one can interject the remark that, if there are such pads, no more should be purchased, but that they should be replaced with rubber pads. Hobbies, such as stamp collecting or making model trains or airplanes, may involve the use of glue or other substances to which a child may be sensitive.

Reactions to drugs must be carefully recorded. Fortunately for the pediatrician, these are much less common in children than in adults. Sensitivity to aspirin is rarely encountered, and I have never seen it in the severe, fulminating form in which it may occur in adults. It is essential to keep this portion of the child's history up to date and to note on the allergy history sheet new drug disagreements as they are discovered. The subject of drug allergy in children will be discussed in detail later on.

Other subjects in the history form, not discussed above, are self-explanatory.

PHYSICAL EXAMINATION

After completion of the history taking, the highlights of which have been indicated, the next step is a complete physical examination. This is done in the routine manner with special attention being given to the allergic manifestations. These will be discussed hereafter as the individual diseases are considered.

In the case of skin disease, it is particularly important to ascertain that the condition is of allergic origin. If there is any doubt, the child should be referred to a dermatologist who should decide the question. If this is done, the pediatric allergist will not then be accused of subjecting to an allergic study patients with such conditions as scabies, pediculosis, psoriasis, lichen and perhaps other diseases.

While the diagnosis of allergic cutaneous conditions can usually be made without difficulty, errors may occur. In this connection the following case report is of interest:

CASE 5093. This boy was five years old when first seen because of "eczema." The lesion had been present on the penis and surrounding area almost since birth. The pediatrician had stated that because the child would outgrow the eczema by the time he was five years

old, the mother should do nothing about it. However, at four and one-half years of age, the condition appeared worse, if anything, and the mother was concerned about the child's not living up to her pediatrician's time table. There was, in this particular case, nothing in the child's personal history or in the family history to suggest allergic disease, and on inspection the condition proved to be psoriasis.

For the purpose of recording the nature and extent of the cutaneous lesions, rubber stamps applied to the physical examination sheet are helpful. Two sets of stamps are used, one conforming to the configuration of the infant and the other to that of the older child. These were first described (2) a number of years ago. Stoesser (7) also employed somewhat similar figures on his record sheets.

PROGRESS NOTES

Progress notes are, essentially, a continuation of the history. The parent should be carefully queried between visits for skin testing and other purposes as to how the child has done in the interval, what has been the effect of the medications prescribed, etc. In the case of older children who come to the office periodically by themselves, one must remember that such children, no matter how poorly they are getting along, will often when queried in the routine manner, say that they have done well. It is always best to check periodically with the parents under such circumstances. One's own patients, if doing well, should come in with their parents at least twice a year for questioning and examination. In the case of out of town patients, such visits are desirable every three or four months, at least during the first year of treatment. One of the most important things which the allergic study should accomplish is to educate the parent to look at the child through the eyes of the allergist. The mother will eventually find the answers to the questions which were previously asked in the formal history taking and in the follow-up notes: "What foods do you know actually bother the child?" "What contacts?" "What drugs?" "What meteorologic factors?" This constant search for relevant factors should be encouraged. Carefully taken progress notes should be considered part of a continuing diagnostic survey, and not merely a record of the effectiveness of therapy.

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CHAPTER 4

SKIN TESTING

THE PARENT often has the idea that cutaneous testing is a scientific procedure of great accuracy by means of which it is possible to determine exactly what causes the child's trouble. It is important to explain in advance that such is not the case. It should be explained that skin testing is merely a laboratory procedure, which, in spite of the drama attached to it, is of considerably less value than a carefully taken history. Testing is necessary because it often gives aids which are time-saving and of great help in the conduct of the case. Like the physical examination, fluoroscopy, and other tests, it is just another aid in the diagnostic study.

It is unnecessary to do tests with substances known to disagree with the patient except for the purpose of checking the reactivity of the patient's skin. For example, if an infant is known to be clinically sensitive to eggwhite and fails to react on scratch testing with eggwhite, it is unlikely that the skin will react to any other foods whether or not the patient is clinically sensitive. The absence of positive skin reactions to food to which the patient is clinically sensitive, is not yet understood. One might suspect, however, that patients might react not to the food itself, but to some immediate metabolic product not reflected in skin reactions. If this occurs, the reason should be explained to the parent who may otherwise assume that skin testing is completely unreliable and not worth doing.

No recent work has been done on the incidence of positive skin tests in nonallergic children. Baker (1) found positive skin reactions in normal children tested by the scratch test practically negligible. Peshkin and Rost (19) in a similar study found that 10 per cent of presumably nonallergic children gave doubtful or positive reactions, the incidence of which decreased as their age advanced. This indicated progressive desensitization to the authors. There have been no studies reported concerning the incidence of positive intradermal tests in non-allergic children. Rackemann and Simon (21) tested

sixty presumably normal adults and found that above half gave positive reactions. Grow and Herman (10), in a group of 150 adults more carefully selected to rule out allergic individuals, found that 55 per cent reacted positively to one or more allergens. Hill (13) as a result of his review of the scanty literature on this subject states: "It seems fair to conclude that positive scratch tests are not common in normal children or infants, but that positive intracutaneous tests are common in unselected adults who have no atopic symptoms. What their significance is, is another question." This indicates, that skin tests require expert integration with the other studies of the patient.

As a general rule, the reactions of infants and children are not as numerous or large as those of older children and adults. The younger the individual, the more likely a "flare" or area of erythema will occur instead of a wheal. This has, however, the same clinical significance. As early as 1920 Schloss (22) observed that a negative cutaneous test was not conclusive and reported five cases of undoubted sensitivity to cow's milk with persistently negative cutaneous tests. This is particularly likely to occur in pollinosis in infants and children as first noted by Kahn and Grothaus (14). A positive or negative skin test has significance, as a rule, only in association with the complete clinical picture of the patient. I do feel, however, that a very strongly positive reaction by a scratch test to animal hair or dander is always of clinical significance.

A positive skin test may indicate:

1. Present clinical sensitivity to the allergen.
2. Past sensitivity to the allergen which may or may not have been of clinical significance.
3. Potential sensitivity. The patient may be in the process of becoming sensitive to the allergen.
4. Skin sensitivity due to biogenetic relationship (see Chapter 60) with an allergen in the category of 1, 2, and 3 above.

The question is often asked, "What is the lowest age limit for skin testing?" While it is often possible to conduct a case properly without cutaneous testing until the child is one year or more of age, there is no objection to testing at any age. In the case of breast-fed infants six or eight weeks of age, and even younger, the skin will

often react to foods in the mother's diet, and the condition of the infant will generally be improved when positively reacting foods are omitted from her diet. In some infants the skin will often be observed to react to foods which the child has not yet ingested. This is important in that these foods may be avoided in the child's diet as he develops, as will be mentioned subsequently.

The technic of cutaneous testing in infancy and childhood is not particularly difficult. The main problem, of course, is to have the child held as still as possible. The next most important prerequisite is that the tests be done by one skilled in the technic. For cutaneous testing in children up to the age at which they will hold still enough for accurate testing to be done without restraint, about five or six

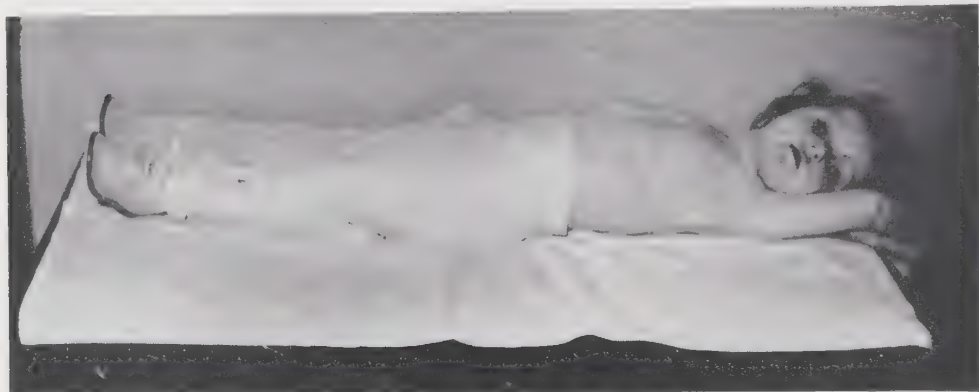


FIG. 4

years, I use a specially devised table. This is a small examining table which has an extensible head rest. All the clothes except the diaper or shorts are removed from the child, who is tightly wrapped in a cotton sheet from just above the hips down to the ankles (Fig. 4). A canvas belt five feet long (152.4 cm.) and fourteen inches (35.6 cm.) wide is now passed over the child's legs (Fig. 5). There are three straps for fastening down this belt. The middle strap is lined up to pass over the child's knees and this must be pulled rather tightly. The other straps may be pulled less tightly, but the lower strap must be pulled tightly enough so that the child cannot work his feet up underneath the belt (Fig. 6).

The mother sits at the head of the table and her task is particularly important. She must hold the child by the elbows which should be held tightly against the child's ears. The child cannot be held

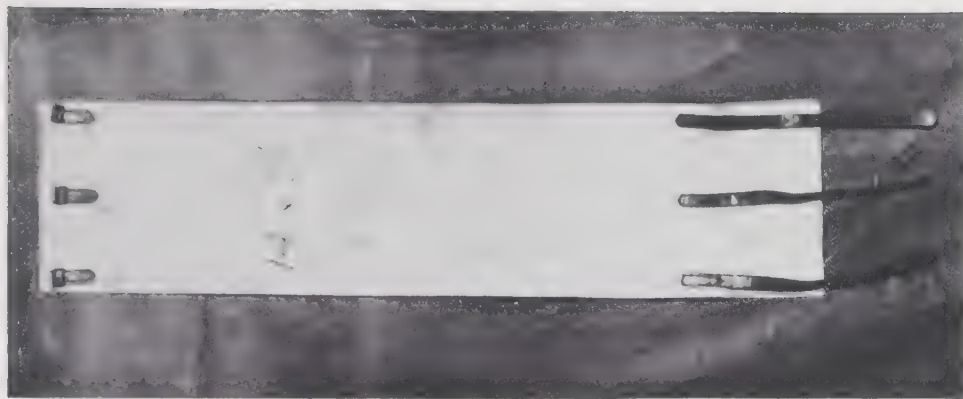


FIG. 5

properly by the wrist, although practically every mother will attempt to do it, and will often persist in attempting despite repeated explanations. A child held in the proper position will still be able to move more or less, but the movements are greatly restricted and tests can be done accurately if the technician is skillful. The tests should be carefully observed and commonly reach their maximum intensity within twenty minutes. Both positive and negative scratch tests are illustrated in Fig. 7.



FIG. 6



FIG. 7

It is my practice in any age group to do scratch tests first. The advantages of this are so apparent that it is difficult to understand why many allergists do only intradermal testing, even in children. The first and most important reason for doing scratch tests is that these are much safer than intradermal tests. There are two deaths from scratch tests mentioned in the literature (26a), but I have never been able to authenticate them. I believe, however, that this can happen. One of my patients, a girl six years old with asthma, who gave a history of exquisite sensitivity to fish, went into severe anaphylactic shock which for a time appeared as though it might terminate fatally, when she was by error scratch tested with the extracts of three different fish at the same time. On the other hand, several deaths in children as well as adults resulting from intradermal testing are mentioned in the literature (11), and many more deaths have occurred which have never been reported.

The second reason for doing scratch tests first is that they may eliminate the necessity for doing many intradermal tests. If the reaction to the scratch test is positive, then it is evident that an intradermal test with that particular substance is not necessary. On the other hand, if the reaction to a properly performed scratch test is negative, an intradermal test may be safely performed with the strongest available material which will not give a nonspecific, irritative false positive reaction. This will eliminate testing with serial dilutions of potent allergens, such as cottonseed, for example.

With scratch tests as with intradermal tests, false positive reactions are much more likely to occur than false negative reactions. It is exceedingly important to check positive reactions, whether from scratch or intradermal tests, repeatedly to make sure that the reaction is actually positive and is not a false positive.

A third reason for doing scratch tests first is the greater irritability of the skin of children. While intradermal tests to inhalants are more reliable than scratch tests, intradermal tests to foods (with the exception of eggs, fish, nuts and seeds) will give many more false positive reactions than scratch tests. This is particularly important in children, although the same experience applies to adults. Not infrequently children are studied who have previously passed through the hands of an allergist who uses only intradermal tests. When one asks the mother about the results she states that she was told that the child gave positive reactions to "everything." Of course, reporting that everything causes positive reactions is practically the same as saying that everything causes negative reactions, for all the value such tests have. However, not infrequently, these children may be satisfactorily tested by means of the scratch method.

The instrument preferred for making the scratches is a leather punch adapted for this purpose by Hill (12). This is a metallic instrument about the size and shape of a small pencil, with the lead replaced by a circular opening a little more than 2 mm. in diameter (Fig. 8). The edges are fairly sharp so that with one quick rotary motion a small circular scratch is made in the skin. The advantages of this instrument are several. In the first place, it does not look like a knife or cutting instrument so that a child is not frightened by its appearance. Second, the scratches are always the same size and shape. Third, it is difficult to traumatize the infant with this

instrument unduly so that, if the child makes a quick movement while the scratch is being made, little damage can be done. With experience it is possible to make these scratches rapidly and accurately, even in a small infant who is struggling more or less in spite of the restraint. Hill* himself no longer uses this device, preferring instead a three-cornered needle. This emphasizes the fact that it is



FIG. 8

of little importance what type of scratching device one employs as long as one is expert in its use.

A buffered isotonic sodium chloride solution (6) is used for dissolving the powdered allergens applied to the scratches. The procedure is, first, to drop this liquid on the scratch. Then the powder is applied and rubbed in with a toothpick, a fresh end being used for each test. By putting the liquid on before the powder, there is less chance of shaking the powder away from the scratch by the struggling of the child. Unbuffered isotonic sodium chloride solution may be used as well as the buffered solution. I do not use the tenth-normal sodium hydroxide solution recommended by many because I feel that this solvent often acts as a non-specific irritant. When glycerinated extracts are used evaporation is minimized and because of its viscosity this material stays in place better than the aqueous

* Hill, L. W.: Personal communication to the author.

solution. However, many false positive reactions are given by glycerinated extracts; positive tests should be repeated several times and always well controlled.

The most common errors in the technique of scratch testing are:

1. *Scratches too close together:* The optimum distance between scratches is about 2.5 cm. (1 inch).

2. *Scratches too long:* If the ordinary scarifier, such as a needle or knife blade, is used the optimum length is about 5 mm. (3/16 inch). With the Hill scarifier this error does not occur.

3. *Scratches too deep:* They should not draw blood because this clots in the depths of the scratch and prevents absorption of the allergen by the lymphatics.

4. *Scratches of irregular length:* This is the mark of an amateur. It will not occur with the Hill instrument.

5. *Too much material used:* Only enough should be employed to cover the actual scratch itself.

6. *Too much "smearing":* The only part of the skin to which it is necessary to apply the material is to the scratch itself; not the surrounding area of the skin.

7. *Testing material allowed to dry out before the test is read:* This prevents absorption of the material into the lymphatics.

INTRADERMAL TESTING

The relative merits of scratch and intradermal testing will not be considered here. This discussion may be found in any of standard textbooks on allergy. Intradermal tests are useful, and in general reliable, for obtaining additional information regarding skin sensitivity only when scratch tests to certain substances are negative. These are principally the following: pollen, cottonseed, dust, flaxseed, fungi, India gum, kapok, orris, pyrethrum, seeds, silk, sera, and epidermoids. Intradermal tests with foods are so unreliable that I test only with fish and egg, except when doing passive transfer tests. If the history suggests clinical sensitivity to any allergen, intradermal testing must be carried out with great care to avoid generalized reactions, double checking the scratch test to make sure that it is negative before doing the intradermal test. Skin tests to bacterial vaccines may be performed, but, as indicated by Swineford (24), have little or no significance. Intradermal tests should not be done to allergens to which the patient is positively clinically sensitive even if

the scratch test is negative. To carry out such tests is an invitation to a generalized reaction.

Intradermal tests, like scratch tests, if positive, should be double checked unless corroborated by the history. They should be done on an extremity so that if a generalized reaction occurs a tourniquet may be placed proximal to the test site to slow down the absorption of the antigen. The treatment is the same as for a generalized reaction on pollen injection (see Table XV). As a rule, generalized reactions will almost never follow intradermal tests to allergens to which an individual is exposed daily, such as house dust, wool, etc., or foods ingested daily, like wheat, milk, etc. Nevertheless, it is a safe principle never to do such intradermal tests unless the scratch test has been negative.

It was formerly stated that material for a properly performed intradermal test should be introduced in the epidermis just above the stratum papillare of the corium. Taylor (25) has shown that it is impossible to do this except on certain areas where the skin is very thick, for example, parts of the soles of the feet. All intradermal injections for skin testing are, therefore, really injections into the corium.

The most common errors in the technique of intradermal testing are:

1. *Testing with allergens which gave definitely positive reactions to the scratch test:* This may precipitate a generalized reaction, as stated above.

2. *Tests too close together:* The optimum distance between scratches is 2.5 cm. (1 inch).

3. *Too much material injected:* The optimum amount is about 0.02 cc. This cannot be accurately measured but is the quantity required to produce a barely visible wheal.

4. *Injection of air with the test material:* This produces a "splash" reaction which is sometimes falsely diagnosed as a positive test.

5. *Injections too deep:* This may result in a false negative test.

6. *Too many tests done at one time:* If there are many positives this may result in a summation effect causing a generalized reaction. The maximum number of tests done at any one time is eighteen for an adult and children according to size. If the tests are nega-

tive or even if positive and the patient experiences no disagreeable reactions, further testing may be continued at the same visit.

7. *Injection into a lymphatic vessel:* This is quite uncommon. The distended lymphatic vessels may give the impression of the pseudopodia of a strongly positive test.

The question arises as to how many tests one should do. There is no truly sound objection to the practice of many of making tests with everything conceivable for which test material may be prepared because, on rare occasions, a positive reaction will be elicited by some allergen which appears to have no connection at all with the case. On closer investigation it may be found that this is one of the substances which is really causing trouble. However, this happens so rarely, and the diet and environment of the infant and child are so limited as compared with those of the adult patient that I feel it is an injustice to subject these children to so-called complete testing. One should test for those substances indicated by the history as possible causative factors, as well as for those substances indicated by experience as often causing trouble in this age group. These substances would include all the foods which the child ingests and also those foods which it is planned to feed him next. As an aid for avoiding omission of any allergens with which it might be important to test the child, I commonly give the parent a check list, indicated by Table VIII. The directions on this list are self explanatory.

It will occasionally be observed, as has been mentioned, that a child will react to some food which he has not yet eaten. In most instances this reaction is probably due to a biogenetic relationship between some food which the child has ingested and the reacting food which he has not yet had. This subject will be further discussed in Chapter 60. In such circumstances it does not make much sense to try this food in the child's diet, even though he may not be clinically sensitive to the food at the time it is tried. To do this is an invitation to trouble. The child should also be tested with house dust, wool, silk, feathers, cottonseed, kapok, flaxseed and those other allergens which are particularly indicated, as mentioned previously, by the history of the case. In this age group flaring occurs oftener than whealing but is of equal diagnostic significance. There is no such thing as a standard-sized flare or wheal applicable to every patient

TABLE VIII
ALLERGEN CHECK LIST

Ragweed	Cashew	Herring	Quince seed	<i>Fungi</i>
Plantain	Cat dander	Hog dander	Rabbit dander	Alternaria
Timothy	Cattle dander	Hops	Radish	Aspergillus
Goldenrod	Cauliflower	Horse dander	Raisin	Dermantium
Art. vulgaris	Celery	Horse radish	Raspberry	Hormodendrum
Pyrethrum	Cherry		Rhubarb	Manilia
Horse serum	Chicken	India Gum	Rice	Mucor
	Cinnamon	Jute	Rye	Penicillium
	Clam	Kapok		Yeast, baker
Cocklebur			Sago	Yeast, brewer
Corn, cult.			Salmon	
Lambs' Quart.	Cocoa (choc.)	Lamb	Scallop	
Pigweed	Cocoonut	Lemon	Sheep dander	
Sheep sorrel	Codfish	Lettuce	Shrimp	<i>Vaccines</i>
	Coffee	Lobster		Autogenous
	Corn			
June grass	Cottonseed	Mackeral	Silk	
Orchard grass	Cranberry	Milk, cow	Spinach	Stock
Red top	Cucumber	Casein	Squash	#1
Rice, wild		Lactalbumin	Strawberry	#2
	Date	Milk, goat	Sugar, cane	#3
	Derris	Milk, human		#4
Birch	Dill	Moss, Spanish	Tapioca	
Elm	Dog dander	Mushroom	Taro (Poi)	
Oak		Mustard	Tea	
Maple	<i>Dust</i>		Tobacco	
Poplar	Efron	Oat	Tobacco smoke	
Willow	Efron control	Olive	Tragacanth, gum	
	Flour mill	Onion	Tomato	
Acacia gum	Patient	Orange	Trout, lake	
Alfalfa	Stock	Orris root	Turnip	
Allspice	Barn	Oyster		
Almond	Eggwhite		Vanilla	<i>Insects</i>
Apple	Eggplant	Parsley	Veal	Caddis fly
Apricot		Pea	Walnut	House fly
Artichoke	<i>Feathers</i>	Peach	Watermelon	May fly
Arrowroot	Canary	Peanut	Wheat	Mosquito
Asparagus	Chicken	Pear	Whitefish, lake	
	Duck	Pecan		
Banana	Goose	Pepper, black		
Barley	Mixed	Pepper, green		
Bean, lima		Pepper, red		
Bean, navy	Flounder	Peppermint		
Bean, soy	Fig			
Bean, string	Flaxseed	Pimento		
Beef		Pineapple		
Beet	Ginger	Pistachio		
Broccoli	Glue	Plum		
Buckwheat	Goat dander	Poppyseed		
	Grape	Pork (bacon, ham)		
Cabbage	Grapefruit	Potato, sweet		
Camel dander		Potato, white		
Cantaloupe	Halibut	Pumpkin		
Carrot	Hemp			

Directions

1. Circle anything on this list known to disagree from your own experience.
2. Underline all foods eaten as often as once a week.
3. Check (✓) all foods eaten at any other time.
4. Put X before all foods disliked or suspected of disagreeing.

which is one plus when it measures so much and two plus when it measures so much more and so on. Every child has his own standard of reaction, and one must discover what this is by comparison with reactions which are the least prominent and have no clinical significance.

Occasionally the patient's skin will exhibit a certain degree of irritability on testing and antihistaminic drugs have been reported of value in reducing the irritability of the skin under such circumstances. This subject has been reviewed by Fond (7) who felt that the best results were obtained by the use of chlorcyclyzine hydrochloride (Perazil, Burroughs Wellcome Company) or Di-Paralene (Abbott), administered in a dose of 100 mg. (to adults) on the night preceding the tests. At the time of skin testing unpleasant side reactions, if they occurred, had disappeared but the skin reactivity was found to be sufficiently depressed to give more accurate readings. To be helpful under such circumstances the tests should be repeated several times. I have but rarely found this procedure of value.

PASSIVE TRANSFER TESTS

When, for various reasons which have been enumerated by Walzer (27), it is not advisable to test the skin of the patient directly, recourse may be had to passive transfer testing. This procedure was first reported by Prausnitz and Küstner (20) and extensively studied and developed by Walzer. Briefly stated, it consists of drawing blood from the patient with sterile precautions and pipetting off the serum which is then subjected to complement fixation and sterility tests. One-tenth of a cubic centimeter of serum is then injected into various sites, usually on the lateral aspect of the upper arm, in a suitable recipient. I commonly employ two recipients as there is considerable variation in the way in which individuals react to passive transfer testing, some being unable to accept a transfer at all and some only very poorly. There is no objection to using the father and mother of the patient or any other members of the family who are not allergic, or if allergic, not clinically or skin test sensitive to the allergens with which they are to be tested.

After injection of the serum, the acute reaction is allowed to subside for a period of twenty-four to forty-eight hours. The skin of the recipient at these sites is temporarily sensitized by this procedure

to the same antigen as the skin of the patient. If foods are to be tested, the recipient avoids these for seventy-two hours previous to the tests. These sites may then be tested with the strongest available allergens for intradermal testing. The great advantage of passive transfer testing is that one has a perfect control on a corresponding anatomical site of the recipient's skin which has not been treated with the serum. (For further details regarding the technique of passive transfer testing, consult Vaughn and Black (26b).)

Passive transfer tests are, however, not infallible and have certain definite limitations. Chobot and Hurwitz (3) showed that in a series of children giving positive intradermal skin tests to foods, only 20 per cent of the tests were shown to have clinical significance; 18 per cent of those with skin reactions to foods to which they were clinically sensitive did not transfer, and only 22 per cent of the tests that did transfer were clinically significant.

In infants and children with generalized eczema, which is the principal reason in pediatric practice for doing passive transfer tests, I now prefer, when practical, to first clear the child's skin with ACTH or cortisone and then test the child directly. These drugs do not significantly influence the results of direct skin testing (9) and I find direct testing much more informative than passive transfer testing.

SKIN TESTING IN THE NEWBORN INFANT

Balyeat (2) stated that he tested the skin of 119 newborn infants with wheat, egg and milk and found two specifically sensitive on the second day of birth. In a series of tests performed by Weber, Kornfield, and Walzer (4) by both the scratch and intradermal methods in over 100 newborn infants, non-specific reactions which were far in excess of those usually found in adults were noted. This and subsequent literature has been reviewed by Matheson *et al.* (17) who concluded that the skin of the full-term, normal newborn infant reacts to various dilutions of histamine phosphate with erythema but no wheal formation, as contrasted to the skin of older children where, with the same technic (scratch), whealing was frequent. The skin of both the full-term and premature infant is capable of fixing reagin locally. This is shown by the fact that the skin of these infants may be passively sensitized by the passive transfer method, and the sites so sensitized will react both by the injection and ingestion of antigen.

The newborn period is considered to be the first thirty days of life.* Skin testing at this age is almost always never necessary or of practical value although conceivably it might have some purpose in a case of a breast-fed infant developing allergy as the result of some antigenic food or other substance passing through with the breast milk. In such cases the skin of the infant sometimes reacts on direct testing with this food.

If the patient does not do well the skin tests should be repeated from time to time in the hope of discovering additional allergens which may be significant. A positive skin test may persist long after a patient has clinically recovered or disappear before recovery takes place.

For a very comprehensive discussion of skin testing reference is made to the recent review by Matheson (16).

OPHTHALMIC TESTING

It is occasionally desirable to demonstrate a positive reaction to pollen when the skin test is negative. For this purpose Peshkin (18) devised the dry pollen eye test. This is done by requesting the patient to look upward, pulling down the lower lid to expose the conjunctival sac, and dropping a small amount of pollen (the same amount as would ordinarily be used for a scratch test) from the end of a tooth pick into the conjunctival sac towards the lateral canthus. Pine pollen is similarly dropped into the other eye as a control. The pollen, if tolerated, is allowed to remain in the eye at least five minutes during which time the patient holds the lids shut with a pledget of cotton. At the end of five minutes a positive reaction is indicated by varying degrees of redness and edema of the conjunctivae as compared to the control eye. The pollen, which by then has matted together and drifted towards the inner canthus, is easily removed by gentle manipulation with a cotton-tipped applicator. A drop of epinephrine 1:1000 is instilled into the eye to counteract the reaction if one has occurred.

Shulman (23) has reported ophthalmic testing with dried food allergens especially prepared in a non-irritating ophthalmic ointment in a concentration of 1:10 by weight. He felt that in all groups suf-

* According to definition by the Committee on Fetus and Newborn of the American Academy of Pediatrics, *J. Pediat.*, 28:244, 1946.

ficiently large to permit a valid statistical conclusion the eye test showed itself superior both in detecting an allergic condition and in not reporting a "false alarm" in a clinically negative patient. This procedure awaits further clinical evaluation in children.

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CHAPTER 5

RECAPITULATION

NOW, HAVING examined and tested the child completely, what is the next step? I believe it is then time for the allergist to sit down and evaluate the patient's record carefully. The first thing is to put down the final diagnoses, as well as these can be established. These should be noted on the first sheet of the record so that the cases may be carefully indexed and cross-indexed.

The next procedure should be to write out specific directions for the patient. I do not believe that an allergist who simply examines and makes tests on a patient and then gives the parent a list of the reactions and a brief discussion of their significance is doing his full duty. I am a firm believer in giving the patient highly detailed directions as to the conduct of his own particular case. The objection to the former procedure is that the parent will forget what she has been told; the objection to the procedure here advocated is that the parent often will not read the directions which have been given.

A lesson was learned regarding this and how to combat it, in an interesting manner. At the completion of a study of a child with chronic atopic dermatitis the parents had been given detailed type-written and printed directions as to the conduct of the child's case at home. In the course of many months the fee for this study was not paid. The reason for this, the mother stated, was that, after leaving my office, the child had not improved and so had been taken to a dermatologist who had advised that all wool be removed from the child's immediate environment. The parents did this and, to their gratification, the child's skin rapidly cleared. On a check of the child's office record, which contained a complete carbon copy of all instructions given the parents, it was found that the first paragraph gave specific directions for the avoidance of wool. It was obvious that the parents had not read the detailed instructions which they had been given.

From that time on the office procedure was somewhat different. Specific directions for the patient were still supplied the parent with

forms as far as possible for the avoidance of specific allergens, such as house dust, cottonseed, flaxseed, orris-root, and the various epidermoids. However, when the parent was presented with this information, she was first told that the instructions given always looked like considerably more work and trouble than they actually were in practice. If the directions were carefully followed, she would soon learn which particular instructions were most important to her own child, and the habit of following these would soon become easy. She was further told that even though the directions were extremely difficult to follow, which they occasionally are, it would be well worth the effort, as this may be the only means for relieving the child's difficulty.

The parent was then asked to sit down in the waiting room and read the directions over carefully and was then returned to the consulting room and asked if there were any questions. If the parent had no questions, I began quizzing her to see how much she understood of the directions. In the case of a particularly dull parent or in cases in which there was a great deal of this to be done, a capable secretary is often able to take over much of the burden.

It is my firm belief that one cannot be too explicit in giving complete directions. One never knows just how a patient may be exposed to any one particular allergen. For example, in the directions for avoiding rabbit fur, I mention that some persons occasionally carry a rabbit's foot in their pocket for good luck. One woman whose child had asthma and allergic rhinitis and gave a strong reaction to rabbit dander called up the office in great excitement to state that she had discovered at least one factor in her infant's difficulty. When the child was a few months old, a well meaning relative had given him a rabbit's foot which had become a fetish. The child would not go to sleep without rubbing it back and forth over his upper lip. While removing the rabbit's foot from this child's environment did not answer all the questions in this particular case, at least it went far in solving many of them.

The allergist is very often unfavorably criticized for giving detailed instructions for the patient. Not infrequently I have been asked, after the parent has read over these instructions, "Doctor, do you really expect me to follow these directions in detail? I don't believe it is possible." My stock answer to this question is, "Suppose

your child had leukemia and you believed that by following these directions you would have a reasonable chance of saving your child's life, you would follow these directions scrupulously, wouldn't you?" The answer to that is always, "Yes, of course." The fact that the parent is less inclined to do this in the case of the allergic disease simply signifies that in the parent's mind the cure may cause more discomfort than the disease. This, however, is a problem for the parent to decide, not the doctor. All the allergist can do is to give all the information he has; the degree of application of this information must be entrusted to the parents.

The appendix of this volume as well as the text contains copies of some of the specific directions for environmental control of the more important allergens which I give to my patients. Instructions concerning diet will be discussed in Chapters 60 through 63.

In many instances the referring pediatrician or general practitioner expects the patient to be sent back to him with treatment material and, if injections are required, specific directions for their administration. When the patient comes from out of town and facilities are not available for treatment by an allergist, this is proper as well as necessary. When, however, it is just as convenient for the patient to be treated by the allergist who has made the study, it is often a grave injustice to the patient to be compelled to return to the referring physician for treatment. There is considerably more to the treatment of allergic disease than the blind following of a printed instruction sheet, however explicit the directions may be.

A patient being treated by a pediatrician or other physician under the direction of the pediatric allergist should return routinely to the consultant every three or four months at first, more often if necessary. At such times the patient or parent should bring a record of all injections and other treatments given by the referring physician, together with notes giving his comments. All this can be written on the treatment records sent the physician (see appendix). In spite of specific requests, however, it is often difficult to obtain adequate progress reports from the referring physician, particularly his impression about the patient's *clinical* condition at each visit. Without such notes it is impossible to establish the patient's response and to treat the patient to his best advantage. The physician will commonly note whether or not the patient gets a severe local or general reaction, but

only the exceptional physician will make a note as to the patient's clinical condition. The willingness of the referring physician to record the immediate effects of injections on one hand, his reluctance to record the patient's clinical progress or lack of it on the other, occur so constantly that it probably is a reflection in some way on the training of our physicians in the medical schools or hospitals.

It is my opinion, and this should be explained to the patient, that in the case of most allergies the patient should be under treatment until symptom-free for one year. Treatments should not be stopped, no matter how well such patients appear to be doing, without consultation with the allergist.

One common reason for stopping treatments, which may be the patient's decision alone or the decision of the physician who is not an allergist, is the occurrence of disagreeable reactions to the injections. This is almost never an indication to stop the treatments, but is an absolute indication that the dosage should be reduced to one which the patient can tolerate. If the patient then does not do well the record should be reviewed and some other procedure introduced in addition to or as a substitute for the present treatments. One of the inherent difficulties in treating patients by repeated injections is the fact that the patient (and often the physician who is not an allergist) is inclined to blame everything that happens from falling hair to falling arches on the injections. Generally when a disagreeable reaction occurs following an injection it is usually accompanied by a marked local reaction. However, this is not always true. An injection reaction should be suspected when any unusual manifestation, no matter how bizarre, *always occurs at the same time interval* following the injection. The interval may vary from a few minutes to several days. When this occurs the dose should be reduced or a placebo (normal saline without any additive, such as phenol) administered and the reaction observed. It is not generally known that phenol, on rare occasions, may cause very disagreeable local and sometimes general reactions in the form of severe discomfort. If phenol is used in the fluid containing the allergen, even as little as 0.5 per cent, this should be suspected, particularly if the patient continues to get the same kind of bizarre reaction despite repeated reduction of the dose. Over a period of twenty years I have seen this happen in two adults and in one child.

CHAPTER 6

ALLERGY IN EARLY LIFE

PATHOLOGICAL PHYSIOLOGY OF ALLERGIC DISEASE

ALL ALLERGIC manifestations, in whatever tissues they may occur, are dependent upon abnormal physiological mechanisms, i.e., edema or spasm of smooth muscle, or edema and spasm of smooth muscle occurring together. It is quite likely that the basic abnormality of physiology in allergic disease is edema and that spasm of smooth muscle occurs secondary to edema in the muscle. It is easier, however, because of the manner in which allergic reactions express themselves clinically, to think of them in terms of both edema and spasm of smooth muscle. It is, therefore, evident that allergic reactions can occur wherever it is possible for these phenomena to take place. The major manifestations of allergic disease, however, take place in three principal groups of tissues: the gastrointestinal tract; the respiratory tract, and the skin. It is extremely interesting, as pointed out by Glaser and Edwards (6) that there is an important relationship between these structures in that they are all covered by epithelial tissues; the tissues which separate the person from his environment. It is brought to the attention of every medical student that the epithelium of the deepest alveolus of the lung or of the most hidden niche of the gastrointestinal tract is a direct continuation of the surface of the body and is in fact a body surface. This circumstance, which is demonstrated to the medical student for the purpose of pointing out an anatomic curiosity, may, perhaps, have a deeper meaning. The epitheliums of these three groups of tissue are the buffer tissues by means of which the complex human organism contacts, draws nourishment from and reacts to the environment. Perhaps, since all three epithelial groups with their underlying tissues of mesodermal origin have developed in the process of evolution into buffer tissues, they are, in a way, subject to some of the same peculiarities, and what may cause the allergic reaction of edema in one tissue, may have a tendency to cause edema in the others because of

similarity in evolution and function. This is perhaps why respiratory infections and diarrhea, as observed by Koch and Schwartz (11) are the most common complications of atopic dermatitis. It may also explain why cutaneous tests elicit positive reactions to allergens affecting the respiratory and gastrointestinal tracts as well as the skin. It is also significant in this connection that the major allergic diseases in the human being in the process of development after birth commonly involve these tissues in the order of their complexity of function. The gastrointestinal tract, the most complex, is involved first with colic or other gastrointestinal disorders, then the skin with atopic dermatitis, and, finally, the lungs with asthma.

INTRAUTERINE SENSITIZATION

It is generally conceded that the tendency to allergic disease is inherited. The inherited defect is probably associated in some way with the complex relationships of the hypothalamus-pituitary-adrenal axis. However, just what factors precipitate the appearance of allergic disease in the human being, especially in early infancy, are not understood. It is well known that antitoxins, antibodies, some medications and many other substances pass through the placenta into the fetal circulation. This passage is physiological and not pathological, as noted by Ratner *et al.* (14, 15, 16) as a result of their review of the literature and their own investigations. They further pointed out that this occurs in man, as in the rodentia, probably because there is but a single cell membrane separating the maternal from the fetal circulations. In other animals, as ruminants, where this does not take place, there is a three-cell layer separating these circulations. They were able to sensitize guinea pigs in utero, both actively and passively, depending upon the stage of pregnancy in which the mother was sensitized. On the basis of these experimental observations, Ratner (17) felt justified in explaining allergic phenomena due to specific foods occurring in certain children early in life as caused by the mother's overindulgence in those particular foods during pregnancy. He felt that this sensitized the infant in utero and reported a series of cases in this category. In a discussion of another presentation on this subject by Ratner and Greenburgh (18), Huber mentioned the striking instance of an infant whose mother ate peanuts in large quantities during her pregnancy. The

child was never breast fed and within a short time after birth gave marked skin reactions when touched with peanuts.

Zohn (23) pointed out that Tuft (20), Smythe (19), Walzer (21, 22) and others have taken exception to Ratner's point of view. Bell and Eriksson (3) were unable, by means of passive transfer tests using cord blood taken from the infants of allergic mothers, to demonstrate skin sensitizing antibodies. Such antibodies could be demonstrated in the blood serum of the mothers. Walzer (21) and Caulfield (4) have confirmed these findings. Zohn (23) performed an experiment of a similar nature after sensitizing twelve pregnant women by injection with ascaris extract, a substance which has the property of easily sensitizing normal individuals. Reagins for ascaris extract could be demonstrated in nine of eleven specimens of maternal blood but in none of the eleven specimens of fetal blood. Zohn (24) later performed deliberate feeding experiments, giving excessive amounts of single foods daily to pregnant women, about equally divided between those giving positive and negative histories of allergy. Zohn could not demonstrate any effect upon the offspring from the point of view of sensitization.

However, despite all evidence to the contrary, it is impossible to avoid the conclusion of Ratner and others that the human infant may be born sensitized to specific allergens. It seems likely that this is due to *active* sensitization of the fetus in utero rather than an inherited specific defect of the germ plasm with respect to a particular allergen. In other words, it is probable that what is actually inherited is the *capacity* to become sensitized, not specific sensitivity to a particular allergen. Hill and Sulzberger (10) have shown that 85 per cent of all infants under one year who give positive skin tests react to eggwhite. It is possible in many instances to explain such sensitivity on the basis of egg in the diet of the mother passing through to the infant in her breast milk, or by early feeding of egg to the infant. On the contrary, enough infants react to eggwhite clinically and by skin test who have never been breast fed or given egg in the diet to make congenital (intrauterine) sensitization the only possible mechanism in such cases in the present state of our knowledge. Sensitization by means of food odors (osmyls) is such a remote theoretical possibility in this age group that I feel it need not be considered. Congenital sensitization occurs to egg more commonly than to any

other food but also occurs to cow's milk, as was demonstrated by Glaser and Johnstone (7), and doubtless occurs to some other foods. This is active rather than passive sensitization.

FETAL HICCOUGHS

It is quite possible that the first clinical manifestation of allergic disease in the human being occurs before birth in the form of fetal "hiccoughs," as suggested by McGee (13). These were first described by Ahlfeld (1), and McGee pointed out the interesting fact that De-Lee (9) had written on this subject. Whenever this question is discussed someone always asks how the mother can tell that the baby is hiccoughing in utero. I have been informed by a number of very able women physicians, one of professorial rank in a medical school, who have themselves experienced this during pregnancy, that there is simply no other way to adequately describe these movements of the fetus. Although little has been written on this subject, fetal hiccoughs, while not frequent, are not of rare occurrence. McGee reported a series of twenty-one such infants, most of whose mothers were allergic, and in approximately 25 per cent it was possible to produce hiccoughs in the fetus by feeding the mother certain foods. The infants generally developed allergies during the newborn period or very early in life. These interesting and important observations, which tie in very nicely with Ratner's theory of active sensitization in utero, await confirmation by other investigators.

URTICARIA

The first clinical manifestation of allergy in the newborn human being is urticaria. This may occur during the first days of life and is manifested by transient rashes, usually with only small wheals and larger flares. It is often unnoticed and rarely commented upon except by the student nurse on the outlook for impetigo. I have never known urticaria during the newborn period to be a troublesome problem and no mother has ever mentioned this in giving a history. The urticarious rash usually disappears within a few days. In many instances the urticaria may be due merely to vasomotor instability secondary to mechanical or thermal stimuli. In other instances it may be an allergic urticaria representing in some way a reaction to the immunological processes going on as the child adapts himself to

the extrauterine environment. It may also be a reaction in breast-fed babies to foods passing through in the breast milk, as will be discussed subsequently (Chap. 44).

A papular type of urticaria of unknown origin may also occur in the newborn. Finlay and Bound (5), because these papules so closely resemble the papules of staphylococcal pyoderma, prefer to term this condition "pustular urticaria." The differential diagnosis from staphylococcus pyoderma may be made by staining the contents of a papule. The cells will consist principally of eosinophils in the case of papular urticaria and neutrophilic leucocytes in the case of staphylococcus infections. If the urticarial papule has become secondarily infected, a mixed picture will be seen. Papular urticaria subsides spontaneously and requires no treatment. Its relationship to the development of future allergic conditions has not been determined.

ERYTHEMA NEONATORUM

There appear to be two main types of erythematous rashes in the newborn, both of which are termed erythema neonatorum. One consists of a diffuse, generalized redness, the cause of which is unknown, which is transient and disappears twenty-four to forty-eight hours after birth. The second type of rash is usually called erythema neonatorum toxicum. The literature on this subject has been reviewed by Levy and Bagner (12) who state that the condition is seen in otherwise healthy, newborn infants and is characterized by edema of the eyelids, erythema of the cheeks, and patchy erythematous macules or a morbiliform eruption on the thorax, abdomen and extremities. There are no systemic manifestations. The authors quoted an incidence of 46 per cent in a group of 1500 infants studied by Mayerhofer and an incidence of 5 per cent in their own series of 1700 newborn infants. They were unable to explain the difference in incidence in the two series.

Levy and Bagner accept the theory of Mayerhofer that the disease is of allergic origin. If true this would be important as one of the first manifestations of allergy in the human being. Anderson (2), however, states that the etiology of this condition is obscure, and while it might be due to some type of hypersensitivity, it has also been attributed to irritation by contact with clothing and oil or soap used for cleansing. It is also my opinion that the condition is prob-

ably due to the latter factors. Formerly the newborn were treated rather vigorously from a dermatological standpoint, being washed free of the vernix shortly after birth and the skin treated with various preparations for the purpose of preventing infection. In my own nursery at Genesee Hospital where practically nothing other than a minimum amount of cleansing is done immediately after birth and only a mild baby oil with a proven non-irritating antiseptic is used (8), such rashes are almost completely unknown. I do not believe that they should be seriously considered as allergic conditions.

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CHAPTER 7

GASTROINTESTINAL ALLERGY

BY GASTROINTESTINAL allergy is meant an allergic reaction in an organ of the gastrointestinal tract. While such reactions most commonly occur from foods, they may also be produced by allergens of other origin, for example, ulcerative colitis due to pollen as described by Rowe (8). By food allergy is meant an allergic reaction caused by food, regardless of the tissue in which it occurs, as atopic dermatitis in infancy due to the ingestion of egg.

Conditions which may be classified under the heading of gastrointestinal allergy in pediatric practice are indicated in Table IX.

TABLE IX
CLASSIFICATION OF ALLERGIC GASTROINTESTINAL CONDITIONS
IN PEDIATRIC PRACTICE

I. <i>Lips</i>
(a) Circumoral contact type dermatitis.
(b) Cheilitis.
II. <i>Gingiva</i>
(a) Contact type gingivitis.
(b) Dilantin sodium hyperplasia.
III. <i>Tongue</i>
(a) Geographical tongue.
(b) Contact type glossitis.
IV. <i>Buccal Mucous Membrane</i>
Contact type stomatitis.
V. <i>Stomach</i>
Pylorospasm.
VI. <i>Intestines</i>
(a) Gastroenterospasm (colic).
(b) Celiac syndrome.
(c) Appendicitis.
(d) Ulcerative colitis.
(e) Intussusception.
VII. <i>Circumanal Contact Type Dermatitis</i>
VIII. <i>Miscellaneous</i>
(a) Angioneurotic edema and urticaria.
(b) Anaphylactoid purpura.
(c) Abdominal migraine.
(d) Cyclic vomiting.
(e) Aphthous stomatitis.
(f) Erythema multiforme.
(g) Subjective and objective symptoms not associated with organic disease—nausea; vomiting; diarrhoea; constipation; singultus; pyrosis; belching; etc.

Except for a relatively small number of disorders, which will be discussed subsequently, the principal symptom in a child (or adult) is abdominal pain. According to Ratner (7), allergic abdominal pain may be initiated by spasm of gastrointestinal smooth muscle, spasm of the small vessels of the intestinal wall, wheal formation in the gastrointestinal wall, or a combination of all these factors. As an infrequent diagnostic feature, the pain produced by such mechanisms sometimes may be relieved by an injection of epinephrine. The various types of abdominal pain due to allergy differ clinically only in degree and have been classified by Fries and Merrill (4) and by Ratner (7) as follows:

1. *Abdominal Pain as a Minor Symptom.* Children may occasionally complain vaguely of abdominal pain which may or may not be severe enough to interfere with their usual activities, but which is nevertheless disturbing to the parents. Tension (not allergy) is one of the most common causes of pain of this type in young children and is often overlooked. It must be considered most seriously in the differential diagnosis. This occurs when the child is faced with a situation which he fears or dislikes. The young school child may have puzzling abdominal pain every morning before school starts, if the problem lies in a school situation. This pain miraculously disappears on Sundays unless he has a problem in Sunday school. The child who is forced to eat may have such pain before meals. There are many other similar situations and this is usually easily diagnosed if it is suspected by the physician.

The differential diagnosis of abdominal pain as a minor symptom of allergy may often be exceedingly difficult. Allergy may be suspected if there is a positive family or personal history of allergy. The presence of an eosinophilia in mucus of the stool is very strong suggestive evidence. Skin tests are almost never helpful. Complete roentgenological studies may be strongly suggestive of allergy, as will be described below. Offending foods may be found by the use of elimination diets. A number of such cases in my own practice have been due to egg, milk and chocolate, but usually only one of these. At times such pain may accompany an acute attack of urticaria or asthma and represent intestinal manifestations of the allergens causing the attack. Very often the abdominal pain is overlooked as one's attention is distracted by the urgency of the major allergic disease.

2. *Abdominal Pain of a Subacute, Recurrent Nature.* In such cases it is highly essential to make a differential diagnosis, and this is attended with the same difficulties and made in the same manner as (1). The most common diseases to be ruled out are chronic appendicitis, disorders of the genitourinary tract, and various non-allergic intestinal conditions, such as congenital anomalies.

Fries and Merrill (4) have described the location and nature of the abdominal pain of allergic origin as fairly characteristic. The child usually points to the region of the umbilicus; occasionally other areas are designated. The pain is cramp-like in character and its duration may be from a few minutes to several hours and may recur at intervals of weeks, months, or longer periods. There may be associated gastrointestinal disturbances such as nausea and constipation, and other symptoms more suggestive of allergy such as diarrhea, especially if accompanied by excessive mucus, and urticaria. Typically, there is no fever.

3. *Severe Abdominal Pain Simulating a Surgical Condition.* Fries and Merrill (4) reported forty instances of children hospitalized as surgical emergencies because of abdominal pain and who were discharged without surgical intervention. One-fourth of these children appeared to be of the allergic constitution and their records included most or all of the following characteristics: (1) a family history of allergy; (2) a past personal history of allergy; (3) a previous history of gastrointestinal symptoms or previous food sensitivities; (4) eosinophilia, and (5) atypical or negative findings on physical examination of the abdomen. Heyl (6) reported an eleven-year-old girl operated upon for suspected appendicitis. At operation the appendix appeared normal. Later allergic gastroenteritis was diagnosed. Ratner (7) pointed out that whereas the allergic reaction *per se* is reversible, the edema produced may result in bacterial invasion and infection resulting in irreversible changes indicating surgery. As far as appendicitis is concerned, Dutton (2) has presented considerable evidence in support of this point of view.

ROENTGENOGRAPHICAL EVIDENCE OF GASTROINTESTINAL ALLERGY

Fries and Mogil (5) studied thirty children following the ingestion of barium meals containing foods to which they were sensitive. The most frequent gastric finding was hypotonicity with delayed empty-

ing. Alterations in the small intestine pattern were infrequent and, when present, consisted of increased segmentation or, in rare instances, accelerated motility. Hypertonicity of the traverse and descending colon was an infrequent finding. Rectal instillations of allergen-barium mixtures produced constriction of the colon or, occasionally, dilatation. Proprietary barium mixtures containing small amounts of flavoring foodstuffs, produced changes in the roentgenograms of children sensitive to those foods.

Fries (3) also used the same technique to study allergic reactions in the stomach, with special reference to the pylorus. He pointed out that the pylorus is a thick, contractile muscular organ with a narrow lumen and large mucosal folds. Embryologically the pylorus is a separate organ and it is therefore logical to find it acting independently of or at variance with the stomach. In response to an offending allergen, Fries observed that the mucosal folds of the pylorus enlarge (edema). This is doubtless accompanied, in some instances, by pylorospasm (which cannot be demonstrated roentgenographically) resulting in narrowing and obliteration of the pyloric canal. Allergic reactions occurring in the stomach following intentional feeding of antigenic substances are most pronounced in the pyloric area. The transient abnormalities thus produced may sometimes resemble fixed organic lesions, and in the interpretation of abnormalities of the pylorus, as revealed by the roentgenogram, the possibility of allergic involvement must be considered.

Adams (1) has presented evidence that mixtures of allergens with barium may produce nonspecific abnormal patterns of morphology and motility in the small intestines which may be incorrectly interpreted as allergic reactions. These are dependent upon physical reactions between the allergens and the barium. She concludes that a gastrointestinal series with a mixture of an allergen and barium can at the best be only circumstantial evidence of gastrointestinal allergy, just as are other tests for allergy. Extreme care should be taken in interpreting radiological evidence and very critical appraisal is indicated.

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CHAPTER 8

COLIC

OUR FUNDAMENTAL knowledge of what is termed "colic" is so uncertain that it is appropriate in discussing this subject to quote a remark by Tenney (20), "And so it is with colic; maybe there is no such thing, but there is certainly something that makes some perfectly healthy babies cry almost unbelievably loud and long without interfering with their perfect health." The importance of colic to the pediatric allergist is emphasized by the work of Martin (11) who noted that the incidence of this disorder in allergic families is about twice that in non-allergic families, and that where both the mother and father have allergic disease he found that 72.8 per cent of the offspring suffered from colic. The overall incidence of colic in his pediatric practice, which is of a general nature, was 36.1 per cent.

This condition, so important in the private practice of pediatrics, has received almost no attention in clinics or institutions caring for young infants where, although apparently infrequent, as pointed out by Levin (9), colic does occur. It is commonly overlooked because of failure of the nurse to call the attention of the attending physician to the crying babies and failure of the physician to diagnose the condition correctly. Colic, in varying degrees of severity, occurs so commonly that it may be considered in most instances as a physiological phenomenon. It generally starts during the first weeks of life and terminates, regardless of therapy, by the time the infant is three months of age, hence the lay term "three-months' colic." Usually the cases coming to the allergist have persisted for a much longer period; the longest in my experience was nine months in one instance and a year in another. In neither of these could an allergic etiology be demonstrated.

Colic may be simply defined as a symptom complex of early infancy characterized by evidence of intermittent abdominal pain of varying degrees of severity for which no organic or obvious physio-

logical cause can be demonstrated. The chief symptom is crying and this may be almost a constant feature so that the family life is disrupted, the parents and the doctor are driven to distraction, and what should be a very happy experience is transformed into a disagreeable nightmare. Some allergic colic may be accompanied by melena (16). Fortunately such cases are not common, but they do occur and are the type usually referred to the pediatric allergist for study because all other measures of treatment have failed.

It is necessary to make a differential diagnosis of colic from distress caused by improper feeding, or pain caused by otitis media or pyelitis, or surgical conditions, such as appendicitis, Meckel's diverticulitis, intussusception, etc. The etiology of colic is not at all well understood. The very fine study of Levine and Bell (10) indicates that, in many instances, the crying of infants may be due to an unsatisfied need for adequate oral gratification, or from abdominal pain caused by spasm of intestinal muscles resulting from the general hypertonicity of the infant. They reported remarkable relief by the use of the pacifier. Brackett (3) suggests that colic may be caused by an excessive volume of contents in the terminal ileum due to hypertonicity of the ileo-colic sphincter, which in some cases may be congenital in origin, and suggests treatment by reducing the volume of food. He draws an analogy between spasm of the ileo-colic sphincter and pylorospasm. Unexpectedly, colic occurs more commonly in the breast-fed than in the bottle-fed baby, according to Brenneman (4) to whom reference is made for a very vivid description of the clinical picture of colic. Colic is probably related in some way to normal developmental processes in the gastrointestinal tract, the nature of which is not clearly understood. The best evidence to this effect is the work of Pierce (13). He observed that the onset of colic, which in full-term infants usually starts at the age of two or three weeks, in premature infants starts at an age commensurate with the degree of prematurity. That is to say, an infant born one month prematurely will not develop colic at the chronological age of two or three weeks, but, rather, at the age of two or three weeks plus one month. This is very strong evidence of a developmental factor, an opinion which Brenneman (4) had previously advanced as his idea of the most logical explanation of colic.

Colic is the first clinical manifestation of allergy in the human

being which rises to a clinical level, i.e., the first allergic disease of which the parents may complain. It occurs at an age when the gastrointestinal tract is first introduced to foreign proteins, either cow's milk or a variety of others which reach the infant in the mother's breast milk. It is, therefore, reasonable to suppose, when one is cognizant of the permeability of the intestinal tract at all ages to unaltered protein (see Chap. 67), that some colic might well be due to sensitization to certain foods. While not all colic is of allergic origin, in some instances it very definitely is. Without going into any great detail, it may be said that the evidence of the allergic origin of colic may be divided into two classes: (1) presumptive, and (2) specific. The presumptive evidence is as follows:

1. There is a definite incubation period of ten days to three weeks after birth before colic develops.

2. During the first weeks of life transient positive reactions to cutaneous tests occur which disappear as the child becomes accustomed to the new foods (5).

3. Transient precipitins to these allergens also occur in the blood stream during the same period (18).

4. Transient blood eosinophilia appears as new foods are introduced and disappears as the child becomes accustomed to these foods (1).

5. Infants who have had colic develop eczema more frequently than infants who did not have colic (19).

6. Eosinophils may be demonstrated in the mucus of the stools of infants with colic. Nance (12) has reported this finding as useful in establishing the allergic origin of colic and a variety of other intestinal disorders. Rosenblum and Rosenblum (15) have confirmed and extended Nance's observations. In my experience this procedure has only occasionally been helpful as it has not been easy to obtain clear mucus from the stools of most infants with colic. However, when an eosinophilia can be demonstrated in the mucus of the stools its significance may be regarded as the same as that of eosinophilia in the nasal smear; the burden of proof is on whoever claims that the condition under consideration is not allergic in origin.

The specific evidence that colic may in some instances be due to allergy is its occasional response to changes in diet. For example, the worst colics will often clear up when the formula is modified. If the

child is on pasteurized milk, he may do better if fed an evaporated milk formula; if he is on evaporated milk, he may do better when given some other type of formula. For substitute therapy, soybean milk is most commonly employed and is highly satisfactory. In those infants who do not respond to soybean milk, an equally good or even superior substitute is an artificial milk whose protein basis is a finely strained meat. These meats are now commercially available, so that this formula, which was first devised by Rowe (16), can be easily put to practical use (7, 8). These formulae will be discussed in Chapter 62.

Before leaving this subject, a few words more about the "incubation period" of colic are in order. If an animal is given an injection of a foreign protein, in the classic case he becomes sensitive to that protein and will react with anaphylactic shock from its reinjection at the end of a given period, usually seven to ten days. Something analogous occurs in the child when the foreign protein is absorbed by the gastrointestinal tract. This is particularly true of cow's milk, the foreign protein most commonly encountered by the newborn infant. Cow's milk is so generally used in the feeding of infants that one often forgets that it is not a natural food for a newborn infant. The only natural food for the newborn infant or the infant during the first few months of life is human breast milk. After thousands of years of domestication, the cow, who rightly deserves the title of foster mother of the human race, still makes milk which is designed primarily for calves and not for human beings. The process of absorption of cow's milk in the gastrointestinal tract leads to a longer latent period than occurs in experimental animals when a foreign protein is injected, so that the incubation period of colic is ten days to three weeks. This leads to a curious phenomenon which is often not appreciated by the pediatrician. The child leaves the hospital with his mother for home just prior to this period. At home, the mother calls her pediatrician, and he usually feels that he can improve on the formula on which the child left the hospital. The formula is changed, and the colic may develop shortly thereafter. Because the formula was changed by the pediatrician, the mother blames him for the child's colic and often turns to some other physician for relief. The pediatrician who is familiar with this phenomenon will, if the child is doing reasonably well, not change the ob-

stetrician's formula but allow the colic to develop, if it is going to, on that formula, and then make the desired changes.

If colic of allergic origin is suspected, skin tests are of no value. Elimination diets with the substitution of cow's milk by soy bean milk or meat milk commonly gives the best results. Such substitute feedings are discussed in Chapter 62. It is, however, well for the pediatric allergist to be thoroughly familiar with the medical treatment of colic, as the patient must be given relief while the allergic studies are being completed. In general, the medical treatment with the usual drugs is unsatisfactory and in severe cases it may be necessary to prescribe narcotics for relief. The only narcotic which I now use when necessary and which has given highly satisfactory relief without complications is meperidine (isonipocaine) hydrochloride (Demerol, Winthrop-Stearns). This may be administered in the form of the elixir which contains 50 mg. per teaspoon (5 cc.). It is often effective in doses of 5 drops and it is very rarely that more than a quarter teaspoon is required. The dose may be repeated every four hours as necessary.*

Before resorting to narcotics, however, other less potentially dangerous drugs may be tried. Atropin, an old time favorite, is almost never helpful, and atropin intoxication has occasionally resulted from its use. Phenobarbital may help occasionally in doses of 15 to 30 mg. ($\frac{1}{4}$ to $\frac{1}{2}$ grain). Elixir of Benadryl (5 cc. contains 10 mg.) in doses of 2 to 6 mg. per pound of body weight per 24 hours is sometimes of value. Dr. William L. Bradford suggested the use of progestin in infantile colic. He felt that the hormone which has a sedative effect on the smooth muscle of the uterus in pregnant animals (and presumably in man), might have a similar effect on the gastro-intestinal tract. (A discussion of this concept may be found in Burrows (6).) His prescription is as follows:

Tablets Pranone (Schering) 5 mg. No. 10.
Sig: $\frac{1}{2}$ tablet twice a day.

Pranone is anhydrohydroxy-progesterone, U.S.P. XIII. If no relief is obtained after ten tablets have been administered, the medication is

* Dr. Frederick J. Martin (personal communication) who has made a study of the dosage of Demerol in colic, recommends a dose of 1.0 to 1.5 mg. per Kg. body weight.

discontinued. If relief occurs, which happens in about 70 per cent of cases, the medication is continued as necessary.

Dr. Joseph H. Fries* in his studies of gastrointestinal allergy in children, reference to which has been made previously, observed that roentgenologists occasionally employ dexedrine to relax the pyloric sphincter. On the basis of this, he prescribed a mixture of equal parts of elixir of phenobarbital (U.S.P.) which contains 15 mg. ($\frac{1}{4}$ grain) per teaspoon and elixir dexedrine sulfate (S.K.F.), an N.F. preparation which contains 4 mg. ($\frac{1}{16}$ grain) per teaspoon. The drug is best administered by a medicine dropper directly on the tongue before feedings. The dose, which is governed by the effect, is one-quarter up to one teaspoon every four hours as necessary. In two infants the use of this preparation caused great excitement but in general dexedrine is well tolerated without excitement in infants and also in older children as indicated by the report of Roberts (14).

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PYLOROSPASM AND HYPERTROPHIC PYLORIC STENOSIS

ACCORDING to Laroche *et al.* (6), what is now called allergy was advanced as a possible cause of pylorospasm by Halberstadt (5) in 1911 and by Lesné and Dreyfus (7) in 1913. However, it was not until 1929 that Cohen and Brietbart (4) suggested that the pathologic condition in infantile pyloric obstruction (including both pylorospasm and hypertrophic pyloric stenosis) is probably identical with that in allergy. Also, that evidences of allergy are present in the majority of cases of infantile pyloric obstruction, and that, depending upon the period of life at which sensitization occurs and the frequency and severity of the shock reactions, there may be pylorospasm with or without organic obstruction. McCarthy and Wiseman (8) in 1929 found an incidence of pylorospasm of 0.8 per cent in a series of 500 infants. They concluded that projectile vomiting, a cardinal sign of infantile pyloric obstruction, when unassociated with disease or malformation, should be considered as an allergic manifestation, and that infants with pylorospasm or pyloric stenosis should be observed later for eczema and asthma. They believed that allergy to cow's milk is a major factor. A most striking example of pylorospasm on an allergic basis was reported by Balyeat and Pounders (1) in 1933. Their case was that of a boy operated upon at the age of four weeks with the typical symptomatology of hypertrophic pyloric stenosis. At operation no pyloric tumor was found. The symptoms recurred and he was again explored with the same preoperative diagnosis at the age of three years and again no pyloric tumor was found. About three weeks after the operation, because of intermittent eczema since the age of three weeks and a strong family history of allergy, he was studied from that viewpoint. He reacted to various foods of which egg and milk were clinically the most important. On removal of these from his diet the abdominal symptoms disappeared in twenty-four hours and the eczema in one

week. It was interesting that, in the discussion of this paper when it was presented to the Southern Medical Society, two physicians reported one case each of an infant with pylorospasm, mistakenly diagnosed and subjected to operation as hypertrophic pyloric stenosis, but later shown to be due to allergy to cow's milk.

Rosenblum (9) described an infant who had a pyloroplasty at the age of one month because of hypertrophic pyloric stenosis. The infant was highly allergic to a variety of foods. The symptoms of pyloric obstruction recurred at the age of three months, and the child was again explored and a pyloric tumor again found. He was again subjected to a Ramstedt operation with good relief. No trace was found of evidence of the first operation. This case strongly suggests that hypertrophic pyloric stenosis may occur secondary to spasm of the pyloric sphincter due to allergy. The evidence to this effect is not entirely limited to infants. Barrie and Anderson (2) reported the case of a twenty-seven-year-old woman who was operated upon for pyloric obstruction, for which a partial gastrectomy was performed. The surgical specimen showed concentric hypertrophy of the muscular coat of the stomach, pylorus and duodenum, with massive eosinophil infiltration of the pylorus and peculiar peri-arterial giant cell follicles. The evidence suggests that this is an example of a true organic intestinal allergic reaction. The woman did not tolerate certain foods well; she had constant blood eosinophilia, and a localized tissue eosinophilia of the pylorus. There were giant cell follicles in the pylorus which closely resembled follicles found in the heart muscle of patients who have become sensitive to neoarsphenamine.

Clinical hypertrophic pyloric stenosis requiring surgical intervention may occur very shortly after birth. One of my own patients was operated upon at the age of two days and a typical pyloric tumor found. If the condition were due to allergy it would mean that the sensitivity of the pyloric musculature developed during intra-uterine life. If we accept the theory of active sensitization in utero, we can accept the fact that substances from the mother's blood, and this could theoretically include a food such as cow's milk, could pass the placental barrier and sensitize the pylorus, the largest mass of functioning smooth muscle in the newborn infant.

It is known, however, that the embryo swallows meconium, cell detritus and hair with the amniotic fluid. At least one of these sub-

stances, meconium, has been studied by Rubovitz *et al.* (10) who confirmed previous observations regarding its irritating effects when it accidentally contacts peritoneum, as on cesarian section and further showed its irritating properties when injected parenterally. On the basis of these observations Bendix and Nechels (3) suggest that possibly the swallowed meconium or some of the other substances may so reflexly irritate the pyloric sphincter that edema and spasm with subsequent hypertrophy may occur. This process might render the pyloric musculature, through some physiological change, susceptible to being sensitized to certain allergens, as cow's milk, mentioned above. An analogy might exist between sensitization of this origin and sensitization of the lungs to various allergens following infection resulting in bronchial asthma. It must be admitted, however, that such theories cannot be taken too seriously in the present state of our knowledge.

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CHRONIC ULCERATIVE COLITIS

ALTHOUGH it has been known for centuries that gastrointestinal disturbances of many types may occur as an idiosyncrasy to specific foods, it was not until 1925 that Andresen (1) first reported food allergy as a cause of ulcerative colitis. The literature with respect to this was later reviewed both by Andresen (2) and by Rowe (20) at about the same time. Both emphasized the importance of the fact that the early pathological changes in ulcerative colitis are practically identical with those produced in animal experiments in allergy by Gray *et al.* (12, 13, 14). Rowe's report is particularly important because it describes two cases of ulcerative colitis in adults due to an inhalant allergen, pollen. Felsen (9) had previously reported upon a patient in whom the sigmoidoscopic picture of allergic colitis could be reproduced at will by local application of high dilutions of the pollen used for the skin sensitivity test to the intestinal mucosa. That this can occur is not quite as surprising as might at first appear since gastrointestinal disturbances, including diarrhea, may not infrequently result from injecting an overdose of pollen extract in the routine treatment of pollinosis.

Lapin and Weissberg (17), as a result of observations based upon sigmoidoscopic studies by Felsen (8) have pointed out the value of this procedure in the differential diagnosis of allergic colitis and chronic ulcerative colitis (non-specific) which may be the result of allergic colitis. By means of this procedure, it is relatively simple to differentiate between these diseases and diarrhea due to fibrocystic disease of the pancreas and celiac disease. According to Lapin and Weissberg (17), Felsen described the findings in allergic colitis as follows:

"The mucosa appears reddened, edematous and is covered with considerable mucous. Bleeding is rare and no visible lymphoid hyperplasia is noted. In some instances actual localized areas of edema resembling wheals may be noted with a surrounding zone of marked

congestion. The appearance in most cases is not unlike that seen in vasomotor rhinitis."

In proportion to the difficult problem which the disease presents, very little has been written on ulcerative colitis in pediatrics. Helmholtz (16), in 1923, first reported on this disease as regards children. He studied five patients between the ages of eight and fifteen years. Borgen, Jackman and Kerr (3) noted that of 871 consecutive cases of ulcerative colitis at the Mayo Clinic, ninety-five patients (10.9 per cent) were afflicted before the age of sixteen years and that one out of every 569 patients registered by the Section on Pediatrics suffered from ulcerative colitis. They suggested that chronic ulcerative colitis is not as uncommon a disease in childhood as is generally believed. However, it might reasonably be expected that the Mayo Clinic would attract a disproportionate number of patients with chronic intractable disease. Elitzak and Widerman (7), over a period of fourteen years at Mount Sinai Hospital in New York, reported a series of twenty-three patients on the pediatric service. In the twenty-six-year period of 1926 to 1952 at the Strong Memorial Hospital in Rochester, New York, 31,555 children were admitted to the pediatric service and of these sixteen suffered from chronic idiopathic ulcerative colitis, an incidence of about one in every 2,000 hospital pediatric admissions. This is an average of about one case every eighteen months which indicates that actually this is a rather uncommon disease in pediatric practice.

The disease may occur at any age. Hart (15) reported a case in a newborn with evidence of perforation which was later shown by post-mortem examination to be due to chronic ulcerative colitis. Beranbaum and Waldron (4) described a male infant first seen at the age of twenty-one days whose symptoms dated from the age of three days. At the age of twenty-four days roentgenographic studies were made with results consistent with a diagnosis of chronic ulcerative colitis, the youngest age at which this diagnosis has been made roentgenographically. The child had a transverse colostomy, did well thereafter and died at the age of eight months following operation for closure of the colostomy. The youngest patient of Elitzak and Widerman (7) was two weeks of age. Smith (22) reported a case which started at three and one-half months of age and did well following an ileostomy at the age of seven months. This was closed un-

eventfully at the age of three years. While the disease doubtless carries a significant degree of mortality, figures for this in children with modern methods of treatment have not yet been reported.

Andresen (2) in a series of fifty consecutive cases of ulcerative colitis in an older age group (ten to fifteen years) demonstrated food allergy as the cause in thirty-three (sixty-six per cent) and these patients were successfully treated by eliminating the offending foods. Of these thirty-three patients, eighty-four per cent were sensitive to milk, 18 per cent to wheat, 15 per cent to tomato, 12 per cent to orange and potato, and only 9 per cent to egg. Rowe (20) also states that milk heads the list of allergenic foods in this disease, but that all foods are suspect. Glaser and Johnstone (11) have reported instances of severe diarrhea in early infancy in infants intolerant both of cow's milk and soy bean milk relieved by the use of substitute milks made with meat as the protein base. It is easy to believe that such infants, if not treated in this manner, might, if they survived, be very good candidates for ulcerative colitis.

The frequent occurrence of other allergic manifestations in patients who suffer from chronic ulcerative colitis has led to the belief that allergy might be a fairly common factor in the etiology of the disease. The more severe cases which have been under our care include a girl who developed bronchial asthma at the age of seven years and ulcerative colitis of moderate severity five months later. One is often startled by the fact that allergy as a possible etiologic factor had never been considered in the past history of patients of this type. In recent years we treated a boy ten and a half years of age who had been suffering severely from so-called idiopathic ulcerative colitis which had started following an upper respiratory infection one year previously. He had been thoroughly studied at several institutions without improvement except that on occasion his symptoms had been relieved temporarily by cortisone. In taking the child's history, we were surprised to learn that the boy had suffered from a fairly severe perennial allergic rhinitis, which began three years before the onset of his gastrointestinal symptoms. With the onset of his colitis nasal symptoms disappeared. While alternation of shock organs does occur, such a complete change-over from nasal to gastrointestinal symptoms is not common. The phenomenon resembles, of course, the better known alternation of shock tissue

which exists between the skin and the lungs, i.e., eczema and bronchial asthma. This has been termed by Ratner *et al.* (19) as the dermal-respiratory syndrome. This particular patient suffered, in addition, very severely from erythema multiforme bullosum, an occasional complication of ulcerative colitis.

Ulcerative colitis is a non-typical disease which shows considerable and unpredictable variations in its course: this makes it exceedingly difficult to evaluate possible etiologic factors on the one hand, the effectiveness of therapeutic measures on the other. While we suspect that ulcerative colitis is caused by multiple etiologic agents, our major therapeutic approach should be directed against the most likely major etiologic factor. If the disease is of allergic origin then the proper elimination of the causative agent will produce improvement and anti-allergic drugs are bound to be effective. In cases of different—e.g., infectious—etiology, allergic management is bound to be disappointing. Every allergist who has treated ulcerative colitis will be able to report cases where a drug which seemed to be ineffective in the treatment of one case proved to be worthwhile in the management of the next. In several instances we have been able to control chronic ulcerative colitis with a medication designed to prevent the effects of histamine. We have been able to relieve several of our more severe cases by using a combination of diethylaminoethyl pentothiazine (Phenergan) and d-catechin. The latter is a chemical derived from flavonoids, an enzyme inhibitor which prevents the liberation of histamine from its precursor, probably histidine (18).^{*} Our own experience in children with this combination seemed to confirm the favorable results obtained by others like Chunn (6) and Schultz (21), yet Segal[†] was unable to duplicate our results in adults.

The same reason which accounts for the lack of consistent results with anti-allergic therapy applies, of course, to the other therapeutic approaches to the control of disease. Anti-infectious medication, for instance, like the azo-compound between salicylic acid and sulfapyridine, which appears to be effective in a fair number of cases

^{*} The combination—catekon-A—was made available to us by Dr. William Swain, Director of Research, National Drug Company, Philadelphia, Pennsylvania.

[†] Personal communication to the author.

which were refractory to allergic management, is likely to be of little value in episodes of allergic etiology.

The advent of ACTH and cortisone has changed the management of the disease. We are afraid that the liberal use of these important therapeutic agents, which control at least temporarily inflammatory reactions of any origin, has retarded the search for the actual etiology of the disease. The allergic component of chronic idiopathic ulcerative colitis, however, is too impressive to be overlooked. This, I believe, is particularly true in cases which have been under my care before ACTH and cortisone became available. I remember, for instance, a three-year-old girl who was referred to us near death. Her illness had started at the age of two and one-half years of age with the gradual onset of bloody diarrhea. The diagnosis of ulcerative colitis had been made after prolonged observation which included repeated proctoscopy. She was referred to us for an allergic survey and admitted to Strong Memorial Hospital. Here she was thoroughly restudied and proctoscopic examinations together with the clinical history and the results of the laboratory tests confirmed the diagnosis of chronic idiopathic ulcerative colitis. A stained smear of the mucus of her stool showed many eosinophils which disappeared as the patient improved. There was also a strong family history of allergy in both the father and mother. Prior to allergic management, the child was given another course of antiamoebic therapy without relief. Skin tests with the common allergens were negative and she was placed on an elimination diet omitting egg, milk, wheat, citrus fruits and tomatoes. She then did very well, having an occasional exacerbation accompanying acute infections but, in general, improving. Because of the persistence of blood in her stools and occasional attacks of inexplicable diarrhea, a psychiatric study was undertaken. No significant recommendations were made, although it was quite evident that occasional emotional upsets caused her to have diarrhea. With these exacerbations, eosinophils were commonly found in the mucus of her stools.

Her apparent clinical sensitivity to foods was lost very gradually. At about the age of five years, egg was carefully introduced into the diet. The introduction of wheat at first caused an increase of diarrhea, but at the age of six and one-half years she was able to tolerate wheat once a week and her tolerance has since gradually

increased. Citrus fruits could be tolerated in small amounts but any attempt to increase to ordinary portions caused diarrhea. When last seen, at the age of nine and one-half years, she was nine pounds above the middle weight for her age and height. She was able to tolerate wheat, small amounts of milk in food, and an egg three times a week. The only times she had significant exacerbations of her colitis were if these limits were exceeded, or if she ate any chocolate, or if she were subject to undue emotional tension.

We also had a very interesting experience with a sibling of this child. He was started on soy bean milk at birth for the prophylaxis of allergy to cow's milk (10). However, at the age of one month this was discontinued because of diarrhea and vomiting. At five months he appeared to tolerate an evaporated milk formula well but only four vegetables, carrots, peas, spinach and squash. All other vegetables caused loose bowel movements. At the age of nine months he gradually developed diarrhea which, by the age of one year, was severe and intractable. He was hospitalized, subjected to starvation and administration of parenteral fluids on which the diarrhea ceased. Laboratory studies failed to indicate an infectious origin for the diarrhea. Smears of the mucous stool for eosinophils were negative.

Because of his history of intolerance to soy bean milk as an infant and the fact that the diarrhea developed while he was on cow's milk, he was put on a pork meat base milk (11) and did remarkably well until the age of sixteen months when transient diarrhea again appeared following herpangina. At this time a geographical tongue was noted which we believe indicates that one is dealing with an allergic infant. When he was two years old, he developed an occasional loose stool and a check of his diet indicated that he was getting egg in some of his foods. These foods were discontinued and when last seen at the age of two and one-half years he was doing well on an egg and milk free diet, and weighed twenty-nine pounds, which is the middle weight for his age and height. It seems reasonable to believe that this boy, if not properly managed, might develop what we consider chronic idiopathic ulcerative colitis.

As in any chronic disease which is highly resistant to all forms of treatment, the psychosomatic aspects assume great importance. This subject has been reviewed by Engel (8). Ulcerative colitis can

undoubtedly be precipitated by the stress of psychic trauma. However, this does not rule out the fact that the disease may be caused by other etiologic factors, such as food allergy. In the treatment of this disease, it is necessary to give all possible factors due consideration. In my experience with children, the allergic factor has been sadly neglected, while overemphasis has been placed on the psychosomatic approach. It is not my purpose to suggest that all cases of intractable diarrhea in infancy and childhood are due to allergy. A differential diagnosis must be made with other diseases of similar symptomatology. It is, however, extremely important to remember that allergy can be a cause of intractable diarrhea and should be seriously considered as a possibility when suggested by the history and, or eosinophilia in the mucus of the stools or when all other methods of approach have failed.

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CHAPTER 11

THE CELIAC SYNDROME

ANDERSEN and di Sant'Agnese (1) described the celiac syndrome as a clinical picture characterized by chronic indigestion and failure to gain weight normally during infancy or childhood. The indigestion results in the excretion of bulky, foul stools containing undigested starch, fat and visible food fragments at some time during the course of the disease. There is chronic or intermittent diarrhea with intervening periods of constipation. The patient develops a "celiac" habitus with a protuberant abdomen, weak, flabby muscles and some degree of wasting. Evidence of a deficiency of one or more vitamins or minerals is commonly found.

The term, "celiac syndrome" is used in preference to "celiac disease" because the clinical picture may have a varied etiology. Andersen and di Sant'Agnese have classified the various forms of the syndrome as follows: (1) true or idiopathic celiac disease based on a metabolic defect, familial in character, the nature of which is as yet unknown; (2) congenital pancreatic insufficiency or fibrocystic disease of the pancreas (mucoviscidosis); (3) chronic dietary insufficiency of severe degree; (4) chronic mechanical obstruction of the pathways of digestion and absorption; (5) chronic enteric infection and parasitic infection of various etiology, and (6) occasional cases of gastrointestinal allergy. There are also other variants as reviewed by Johnstone (6).

Riley (13) noted the association of the celiac syndrome with eczema in one case and stated that this had been previously observed by others. It is, however, to Kunstadter (7) and to McKhann and associates (11) that credit must be given for really initiating the study of the celiac syndrome as a manifestation of gastrointestinal allergy. They demonstrated the allergic nature of certain cases by successful treatment from the standpoint of allergy, the most important single therapeutic measure being the elimination of cow's milk from the diet although occasionally foods other than cow's

milk may play an important part. In 1953 Kunstadter and Schultz (8) reviewed thirty-six cases of infantile diarrhea presenting the celiac syndrome and found that eleven or almost a third were of allergic origin with cow's milk the principal offender. In most instances the infants were able to tolerate the reintroduction of cow's milk into the diet without resulting diarrhea after an abstinence of periods of from three to forty-two months (average 18.3 months), usually at the age of two and one-half to three years.

The evidence that foods allergy may cause the celiac syndrome is steadily mounting. Collins-Williams and Ebbs (3) found that the gluten of wheat starch was a relatively frequent offender. Grette and Imerslund (4) have reported wheat, rye and oats as allergenic foods. Ruffin and associates (16) reviewed the literature of this subject and commented upon the well-known similarities between sprue and celiac disease. They reported an adult with sprue relieved by a wheat-free diet.

Collins-Williams and Ebbs (3) found no significant correlation between the positive skin tests in the celiac syndrome and clinical sensitivities. They concluded that skin testing is of very little value in the etiological diagnosis of the celiac syndrome due to gastrointestinal allergy.

Diarrhea of allergic origin has been particularly discussed by Rothman (15), but in the differential diagnosis of celiac disease all other causes of chronic diarrhea in children must be given due regard. Probably the most important disease to be considered is fibrocystic disease of the pancreas. According to Johnstone (6) this disease may be ruled in or out by one or all of the following measures: (a) an analysis of a fresh duodenal juice specimen for pancreatic enzymatic activity (2) which is absent in fibrocystic disease of the pancreas; (b) an analysis of a fresh fecal specimen for trypsin activity (5) which is always absent in fibrocystic disease of the pancreas, and (c) a study of vitamin A absorption (10). In fibrocystic disease of the pancreas the vitamin A ester is very poorly absorbed and the vitamin A alcohol is well absorbed. Children with idiopathic celiac disease show poor absorption of both the vitamin A alcohol and the vitamin A ester. Johnstone (6), however, has observed that in the allergic celiac syndrome vitamin A alcohol is normally absorbed whereas in idiopathic celiac disease it is not absorbed. This

observation, if confirmed, will prove a valuable aid in screening out those patients suspected of suffering from the allergic celiac syndrome.

Lapin and Weisberg (9) have pointed out the value of sigmoidoscopy in differentiating this disease from idiopathic ulcerative colitis, an occasionally helpful procedure, although blood in the stool does not occur as a characteristic feature of the celiac syndrome.

The mechanism by which the celiac syndrome is produced as an allergic reaction is not completely clear. It is probably due to edema of the intestinal mucosa which interferes with intestinal secretions, absorption and motility. The possibility that allergy is the cause of the celiac syndrome in any particular case must be considered if other causes can be ruled out. It should be particularly considered if there is a family history or a past personal history of allergy. The finding of eosinophils in the stools as described by Nance (12) and by Rosenblum and Rosenblum (14) is strong confirmative evidence. The diagnosis is established if the condition is relieved by elimination diets and if the diarrhea can be reproduced by feeding the suspected offending food or foods as discovered by means of the diet.

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CHAPTER 12

GASTROINTESTINAL ALLERGY

(Continued)

CYCLIC VOMITING

THE TERM "cyclic vomiting" is synonymous with the terms periodic vomiting, recurrent vomiting and acetonemic vomiting, the last designation being preferred by the French pediatricians. The disease begins in early childhood and usually terminates with puberty or earlier. It is characterized by repeated attacks of vomiting which occur at regular or irregular intervals of a few weeks or a few months and may be accompanied by fever, headache, and abdominal pain. The attacks are commonly resistant to any form of treatment and usually disappear spontaneously in the course of several days. A few cases in which the outcome was fatal have been reported with negative findings at necropsy.

The consensus among pediatricians is that cyclic vomiting is not a specific disease entity but is a symptom complex which may result from a variety of causes. Among these may be: infections, especially acute infections of the upper part of the respiratory tract, tonsillitis, chronic appendicitis, and syphilis; metabolic conditions such as allergy, faulty fat metabolism, spontaneous hypoglycemia, adrenal insufficiency, ketosis and fatigue; gastrointestinal disorders, especially intermittent high obstruction, gastro-enteroptosis and constipation, and orthopedic conditions such as faulty posture which results in gastro-enteroptosis. At times it appears to represent an abdominal form of migraine. Cyclic vomiting also occurs in over half of the children who suffer from familial autonomic dysfunction as noted by Riley (11).

Cyclic vomiting appears to be very definitely on the decrease and is now rarely encountered. This is perhaps due to the fact that many of the above conditions which may cause the disease are diagnosed and treated earlier and more effectively than was the case many years ago. I have never seen this disease due to allergy, and a num-

ber of patients referred for allergic study were shown to have cyclic vomiting as a result of faulty ocular muscle imbalance (6). Fries and Jennings (5) have reviewed the literature of cyclic vomiting with respect to allergy and reported six patients of their own wherein this syndrome was precipitated by the ingestion of specific foods. The disease should be suspected of being of allergic origin if it occurs in members of allergic families and if other causes of vomiting can be ruled out. The diagnosis is best made by means of elimination diets.

GEOGRAPHICAL TONGUE

Little attention was paid to the geographical tongue until the middle of the last century when Czerny (4), in developing his concept of the exudative diathesis, emphasized its presence as one of the characteristics of this condition. Weigert (12) stated that, when associated with the exudative diathesis, geographical tongue occurs as a first symptom in about 25 per cent of cases. He further observed that it does not appear during the first two months of life but occurs for the first time mostly in the second and third quarters of the first year and thereafter more infrequently until the 13th month. The youngest patient that I have ever seen with this lesion, however, was six weeks of age.

It is now generally accepted that the modern concept of the "allergic constitution" has replaced the older concept of the "exudative diathesis." This certainly offers a more hopeful approach to a study of the basic factors which are responsible for the clinical manifestations. So far as I can determine, McLendon and Jaeger (9), in 1933, were the first to note that geographical tongue can occur as a symptom of food allergy and found this lesion in about 10 per cent of their cases of milk intolerance. They reported that in some instances it could be produced by feeding specific foods. In a series of 100 allergic children studied over a ten-year period, the "allergic tongue," as Clein (1) termed it, was the first noted symptom in three cases. This type of lesion consists of a circinate, "hive-like," bald area with slightly raised, reddish borders, usually on the edges or tip of the tongue. He regards this to be due to food allergy and states that in later years the lesions assume the appearance of geographical tongue.

I have seen somewhat more than fifty children with geographical tongues and, while no detailed studies have been yet made, have the impression that its presence indicates that one is dealing with an allergic child. In all but a few instances the tongue was called to the attention of the parents, rather than the parents calling its attention to the physician, as is usually the case with easily overlooked physical abnormalities in pediatric practice. In an occasional instance the child would complain of a burning or smarting sensation when the bare areas of the tongue came into contact with tart fruit juices, but otherwise the children appear to have no subjective symptoms. In no instance has a child been studied from the standpoint of allergy because of a presenting complaint of geographical tongue.

OTHER GASTROINTESTINAL ALLERGIC DISORDERS

Occasionally circumoral contact type dermatitis occurs resulting from allergic irritation of the skin of the lips by a food or other contactant. In early infancy this is quite common and is particularly due to spinach and less frequently to carrot, orange and other foods. This type of dermatitis invariably disappears spontaneously in the course of a few weeks. The children do not commonly appear to be harmed in any way by the ingestion of the foods producing this form of dermatitis at this age. Such a type of contact dermatitis in an older child is illustrated in Figure 9.

This seven and one-half-year-old boy was seen in April. The rash was of about four months duration. A fungus infection had been suspected and he had been under the care of a dermatologist without relief. The boy had developed the annoying habit of sticking out his tongue and rotating it about his lips. It was noted that the rash was worse when the weather was cold. It was suspected that the rash was caused by the mechanical action of the friction of the rough epithelium of the tongue on the skin of the lips aggravated by moisture and cold and that the boy had developed the habit of doing this because of the somewhat pleasurable sensation it provoked. All attempts to break the habit failed and the boy and his parents were rapidly becoming psychiatric problems. Although there was nothing in the history to suggest allergy, the boy was, in desperation, placed upon an elimination diet. The response was rapid and gratifying. It was soon found that the rash was due to contact with orange and

with pear juice and on eliminating these from the diet the rash cleared and did not recur. Four years later the boy developed ragweed pollinosis.

Chilitis of allergic origin in young children is quite uncommon and may be due to contact with food. When this is suspected an attempt may be made to have all liquids taken through a straw and to avoid licking the lips afterwards. While this is difficult to accomplish one can occasionally obtain help in discovering the offending



FIG. 9. (RGH) Boy seven and one-half years. Circumoral contact type dermatitis due to fruit juices (pear, orange).

food in this manner. The application of a protective ointment, such as one of the silicote preparations, may occasionally serve as a therapeutic test. In older children the application of cosmetics to the lips may occasionally result in chilitis.

A contact type of gingivitis may occur in very young infants from irritation by rubber nipples. This, however, is very uncommon. In older children gingivitis may rarely be due to foods or from chewing gum. Dilantin sodium hyperplasia of the gums is commonly regarded as an allergic drug reaction but curiously the histological sections show no characteristic eosinophilia (3). Contact type stomatitis and glossitis are very rare in children and, so far as I know, glossodynia of allergic origin has never been described in a child.

Aphthous lesions (canker sores) may be due to food allergy but the mechanism by which this may occur is completely unknown. Chocolate and nuts are the most common offenders. However, I have never seen aphthous stomatitis of the mouth successfully treated as a result of study from the standpoint of allergy. Practically always, the discovery that this is due to a food is made by the patient or his parent. Lesions of erythema multiforme may involve the mucus membranes of the mouth and anal orifice. When this occurs the condition is sometimes called the Stevens-Johnson syndrome. Costen's syndrome (2), a term used to denote a variety of bizzare symptoms, some of which may be suspected of being of allergic origin, and which involve the mouth and adjacent structures, has not been described in children. This syndrome results from reflex disturbances caused by various disorders of the temperomandibular articulation.

Angioedema and urticaria may occur anywhere in the gastrointestinal tract and the symptoms will naturally depend upon the localization. Ladd and Gross (7) have suggested that this may at times cause disturbed peristalsis resulting in intussusception, and such a case has been reported by Marenilli (8). Symptoms produced by anaphylactoid purpura of the gastrointestinal tract will be discussed in Chapter 49.

Perianal dermatitis of the newborn, described by Pratt (10) is probably caused by alkalinity of the stools in susceptible infants (see also Chapter 25). I have never encountered pruritis ani of allergic origin in pediatric practice, but Clein (1) mentioned two cases in his series of 100 allergic children observed over a ten-year period.

In addition to the above discussed disorders there are many subjective and objective symptoms of the gastrointestinal tract which may be due particularly to food allergy and are not associated with organic disease. These are nausea, vomiting, diarrhea, constipation, singultus (hiccup), cardiospasm, pyrosis (heartburn), belching and probably others. Detailed study of these from the standpoint of allergy has not yet been made.

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REGIONAL ENTERITIS

This condition has been thoroughly studied by Van Patter (5) and associates to whom reference is made for a complete discussion. According to these authors, regional enteritis affects mainly young adults and is characterized clinically by abdominal cramps, diarrhea, fever, loss of weight, anemia and perianal abscesses and fistulae. Its lesions are usually limited to the terminal portions of the small bowel but may be found elsewhere in the small intestine and also in the colon. The lesions are characterized by granulomatous, necrotizing, ulcerating and cicatrizing process. Histological findings can be divided into a primary process consisting mainly of lymphatic obstruction and edema suggesting that the disease has a definite pathological picture and a secondary, nonspecific, inflammatory component.

Van Patter and associates (5) state that bacterial, protozoal and viral agents as well as sarcoid, allergy and trauma have all been advanced without conclusive evidence as etiological factors and the current opinion is that none has etiologic relationship to this disease. They state, however, that intestinal allergy cannot be excluded as a possible cause. In studying 600 patients with this disease, they were impressed by the number who claimed that certain foods caused ex-

acerbations, particularly milk. The fact that some of the most desperately ill patients can be restored to normal health and can remain healthy if a certain food is omitted from the diet, they believe is strong evidence of a cause and effect relationship. Some of the vascular changes encountered are those associated with allergic reactions and the entire pathologic process, including the formation of tubercles, is such as to suggest the idea of an allergic etiology of a type related to an Arthus or Schwartzman phenomenon.

Rowe and Rowe (3) have also discussed the possible role of allergy in the etiology of regional enteritis and have reported cases in adults which they feel belong in this category.

Regional enteritis may occur at any age and among the 600 patients studied by Van Patter and associates there were eighty-five between four and fifteen years of age. Storrs and Hoekelman (4) who reviewed a different series of cases, found the records of only twenty-five children with acute regional enteritis and three with the chronic disease ranging in age from birth to fourteen years. They reported eight additional patients of their own with the acute disease. Their studies lead them to agree with an early remark of Barger (1) that acute regional enteritis and chronic regional enteritis are not the same entity.

The clinical manifestations in the acute condition simulate those of acute appendicitis but usually subside spontaneously. Howard and associates (2) have since reported an acute attack in a two and one-half year old girl and the chronic form in a five and one-half year old girl. They feel that not enough long term follow up studies have been done in the acute cases so that it can be unequivocally established that they have no relationship to the chronic disease. They recommend that regional enteritis should be considered in all cases of abdominal pain in children.

It is evident that this disease deserves very careful study by everyone interested in gastrointestinal disease and particularly by the allergist.

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THE ECZEMATOID DERMATOSES

THE CUTANEOUS reactions due to allergy, i.e., the allergic dermatoses, may be simply and conveniently classified as follows:

- I. The eczematoid dermatoses.
- II. Urticaria and angioedema.
- III. Drug eruptions.
- IV. Physical allergy.
- V. Allergic purpura.

VI. The exanthematous diseases. While the exanthems of measles, scarlet fever, etc., are specific allergic reactions to specific infections, they are not ordinarily considered in terms of allergic dermatoses and are included here only for the sake of interest and completeness.

VII. Miscellaneous. Here may be included the skin manifestations of the various collagen diseases, such as disseminated lupus erythematosus, dermatomyositis, periarteritis nodosa, scleroderma, rheumatic fever, rheumatoid arthritis. Also included are non-collagen diseases such as geographical tongue, and other forms of mucous membrane involvement.

The most important of these diseases to the allergist in general and the pediatric allergist in particular is the group of the eczematoid dermatoses. These are the skin conditions which for many years were lumped together under the term "eczema." It is only relatively recently that the various members of this group have been rather satisfactorily defined and separated out although much still remains to be done in this field.

The eczematoid dermatoses are more common in infants and children than in adults because:

1. The skin is more delicate and thus more easily injured by various agents including microorganisms.
2. The glands of the skin are more active and thus the skin is more apt to be irritated by its own secretions.
3. The skin is rapidly exposed to one new foreign protein after

another as the child develops and the diet and environment expand.

While every pediatrician has a fairly accurate idea what is meant when the eczematoid dermatoses are mentioned, there is as yet no simple practical definition for this term. According to Kreibich (3), Hebra, the father of modern dermatology, is said to have inferred that, "Eczema is what looks like eczema." Sulzberger (4) feels that this is not an unreasonable statement even today.

A good definition, favored by Hill (2) and which at least is adequate, is that of Wise and Wolfe (6):

Eczematous eruptions are characterized by polymorphous lesions consisting of: Erythema, scaling, papules, vesicles, and at times Lichenification, accompanied by more or less itching.

Eczema is a reaction form—an allergic response on the part of a susceptible individual to something to which he is sensitive.

THE ECZEMATOID DERMATOSES OF INFANCY AND CHILDHOOD

The eczematoid dermatoses, the skin conditions which look like "eczema," may be classified as follows. This classification is only slightly modified from that of Sulzberger (4) and of Hill (1):

1. Atopic Dermatitis
 - a. Acute (including atopic erythroderma) and subacute.
 - b. Chronic.
 - c. Atopic dermatitis by contact.
2. Seborrheic Dermatitis
 - a. Scaling erythematous type.
 - b. Moist, fissured type.
 - c. Erythrodermia desquamative (Leiner).
3. Contact Dermatitis
4. Eczematoid Dermatoses of Bacterial Origin
 - a. Fungus as epidermophytids.
 - b. Non-fungus.
5. Nummular Eczema
6. Circumscribed Neurodermatitis
(Lichen chronicus simplex circumscriptus Vidal)
7. Combinations of any or all of the above.

These various groups will be individually discussed in the immediately following chapters.

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CHAPTER 14

ATOPIC DERMATITIS

THE TERM "atopic dermatitis" was first introduced by Coca and Sulzberger (2) in 1934. While the word "atopy" may have lost much of its original meaning, except for the single fact that allergy still is a "strange disease," nevertheless, as Hill (4) remarks, "it represents a useful and accurate nomenclature to apply to a well defined clinical and immunological condition which is as much a distinct entity as diabetes is." That the pediatricians do not stand alone in this attitude is indicated by Epstein (3) who states, "The term 'atopic dermatitis' is . . . valuable . . . because it is the only unmistakable term for this form of eczema. For this reason it should be used regardless whether one agrees with Coca's concept of atopy or not."

Atopic dermatitis is the condition most commonly termed "infantile eczema" or "allergic eczema," or "simple eczema" although it is far from being a simple disease. It is the most important skin disease of infancy and childhood. As indicated in Figure 1, most cases (30 per cent) begin at or before three months of age, continue to occur throughout the first two years of life, and occur only occasionally until about six years of age. Thereafter, the incidence of onset is relatively nil.

GENERAL CHARACTERISTICS OF THE CHILD WITH ATOPIC DERMATITIS

There is a great paucity of data on this subject. It is said to be a matter of common observation (5) that the vast majority of these children have blond hair and blue eyes and in all but the involved parts the skin is of a very delicate, fine texture. There is, however, no data bearing specifically upon the relationship of race to this disease. Rochester, New York, has a relatively small negro population, but I believe that in proportion I have seen as much eczema in the colored as in the white race.

Bakwin and Bakwin (1) have reported some very interesting but as yet uncorroborated studies of body build in this disease. They also report that eczema is about twice as common in the male as in female infants. This has been also observed by others. Infants with eczema are, according to the Bakwins, on the average slightly taller and considerably heavier than control infants from the same economic environment. These infants also show definite differences from the controls in body build. The head is larger, due to its greater width. The face is much broader than in the control group and the eyes are more widely separated. Also, as compared with the controls, the lower jaw is higher. The shoulders, hips, and chest circumferences are larger, and the hands and feet are slightly broader.

Bakwin and Bakwin (1) also observed a critical level in the weight-age relationship below which infants are relatively immune to eczema. This, also, is a matter of fairly common observation. The malnourished infant with eczema is generally one who is ill or has been subjected to too vigorous elimination dieting.

It is well established in folklore that the eruption of the teeth is very frequently associated with exacerbations of eczema. Talbot (9) noted that even when all known factors have been properly regulated, erupting teeth may appear to cause a relapse of the skin condition. This is also my experience. Just why this occurs is not known. It is perhaps associated with the pain of teething which appears to be maximum just before eruption and which may act as a stress factor. It may also be due in part to histamine-like substances liberated in the gum tissues by the pressure of the erupting teeth.

Talbot (9) has also observed that children suffering from eczema are likely to have periods of diarrhea associated with improvement of the skin. This happens occasionally, and may be due to elimination of the allergen by the bowels or possibly represents the expression of a common phenomenon of change in shock organ, and occurs not infrequently in allergic disease. The best known of these is the alternation between asthma and atopic dermatitis which has given rise to Ratner's term for this phenomenon, "the dermal-respiratory syndrome."

Strickler and associates (8) studied the gastric secretion in infants and children with atopic dermatitis and concluded that there was no consistent deviation from the normal as regards either free or total hydrochloric acid.

Owings and Riley (6) during the exudative stage of atopic dermatitis noted that the blood serum potassium was elevated in proportion to the total area of exudation and to the acuteness of the process. The blood sodium and phosphorus also tended to fluctuate similarly to the serum potassium and, with improvement of the condition, the electrolyte level tended to revert to normal. It seems unlikely that tissue breakdown is the entire cause of these findings since similar changes have been noted in other atopic disease where tissue destruction is at a minimum. It was suggested that these electrolytic changes may represent potassium and phosphorus mobilization and loss with sodium retention and subsequent water-logging of the shock organ. These electrolytic changes together with changes from other non-specific stresses may have an additive effect in causing exacerbations and prolongation of symptoms.

Williams (10) made the observation that the intramuscular injection of histamine into individuals who have atopic dermatitis produces an increase in the skin temperature at the sites of predilection for this condition, i.e., the face, neck, upper part of the chest, and flexures of the elbows and knees. The increase of skin temperature in normal persons is limited to the face and neck and is not observed in the flexures. It is suggested that the increased reactivity of these sites to histamine when injected intramuscularly may be a factor in the characteristic localization of atopic dermatitis.

One very interesting characteristic of atopic dermatitis is the tendency for this disease to clear in the presence of an acute intercurrent febrile infection. Following measles, particularly, the disease may disappear for a period of as long as two or three weeks or even longer. However, such remissions have never been permanent in my experience. Following measles it is known that the tuberculin test, if it has been positive, may be temporarily reversed. It is possible that the same immunological mechanism responsible for this may in some way also cause the temporary clearing of the skin in atopic dermatitis although the skin may clear, though usually not as completely, in other febrile infections than measles.

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ATOPIC DERMATITIS—CONTINUED

ACCORDING to Hill (3) atopic dermatitis is characterized by: A *hereditary disposition* based on a *constitutional abnormality*.

There is *hypersensitivity* of the *deeper layer of the skin* (true cutis) to *potein or protein-like* allergens. Hypersensitivity to these is usually manifested by *wheel reactions* of the *immediate type* to *scratch or intradermal tests*. Patch tests are usually negative.

Responsible allergens may reach the sensitized tissue by *ingestion* or *inhalation* or by *direct contact*. Passive transfer tests are often *positive*. *Typical sequellae* may occur, often in this order, as the child grows older; recurrent upper respiratory disorders; pollinosis and asthma.

Atopic dermatitis beginning in the early weeks or months of life, commonly starting on the cheeks may be associated with or follow a seborrheic dermatitis so gradually that at times it is extremely difficult to determine when and where one condition begins and the other ends. If the rash spreads it involves next commonly the extensor surfaces of the arms and legs, particularly the lower portions, the popliteal and cubital fossae, the wrists, ankles, and trunk. Practically the entire cutaneous surface except the palms and soles may eventually be involved.

There are three principal forms of atopic dermatitis:

1. Acute, including atopic erythroderma and subacute.
2. Chronic.
3. Atopic dermatitis by contact.

There are four principal stages in the development of the acute and subacute forms of atopic dermatitis, any or all of which may be present at the same time:

1. Congestive stage characterized by simple reddening of the skin. This is called *erythematous eczema*. The chronic congestion may stimulate hypertrophy of the squamous cell layer of the skin causing the so-called *squamous eczema*.

2. *Vesicular eczema* is characterized by the formation of minute intra-epidermal vesicles. These often occur at the tops of small itching papules which may be a prominent feature and leads to the term *papular eczema*.

3. *Moist or weeping eczema*. When the vesicles coalesce and rupture causing serum to exude on the surface of the skin.

4. *Crusting eczema* due to drying of the serum on the skin.

The form which atopic dermatitis will take depends upon the acuteness of the process and other as yet unknown factors.



FIG. 10. (RGH 4220) Boy five months old.
Acute atopic dermatitis.

A child with marked, typical, acute atopic dermatitis is illustrated in Figure 10. The skin of the face is acutely flushed; there has been some exudation of serum with crust formation, and scattered papules as the result of secondary infection from scratching are present. The dermatitis ultimately cleared but the boy developed bronchial asthma. As he was an achondroplastic dwarf with a small chest even mild attacks were very distressing.

CHRONIC ATOPIC DERMATITIS

If the infant or young child does not recover from atopic dermatitis it tends to localize in time particularly in the cubital and pop-

lital fossae, around the wrists and ankles, especially on the extensor surfaces, around the neck and to a lesser extent on the axillary folds. Thus chronic atopic dermatitis, as pointed out by Hill (2), may be regarded as the end stage of acute atopic dermatitis and is the form which atopic dermatitis commonly takes in older children and adults. It is probably due to the anatomical and physiological differences of the skin at the various ages. In this disease lichenification (exaggeration of the normal cross-markings of the skin) is a prominent feature.

Figures 11 and 12 illustrate chronic stages of atopic dermatitis. This little girl did not improve on hospitalization, diet or any other



FIG. 11. (RGH 6312) Girl one year of age with chronic atopic dermatitis. Note the enlarged left axillary lymph node.

form of therapy then known. ACTH and cortisone were not available or they would have been used. In Figure 11, the lesions are most marked on the face and the arms below the elbows and (not illustrated) the legs below the knees; in other words, the more commonly exposed areas of the infant. This suggests atopic dermatitis by contact, possibly from house dust. At the time this child was studied, allergens other than foods were not seriously considered as possible etiological factors. Such a patient today would be thoroughly studied from that standpoint and treated by injection rather than simple avoidance if she reacted to or were clinically sensitive to allergens of this character. Eventually, shortly after these



FIG. 12. Same girl as Figure 11 at the age of two and one-half years.



FIG. 13. (SMH 4220) Chronic atopic dermatitis in a three and one-half year old boy specifically due to wheat.

photographs were made, the parents' business took them to California to live where she slowly improved. It cannot be said with certainty, however, that the improvement was due to the change in climate.

Figure 13 illustrates chronic atopic dermatitis in a three and one-

half-year-old boy specifically due to wheat. It is most unusual for single foods, except egg, milk and fish and a few other less important foods to be the sole cause of atopic dermatitis and this is particularly unusual for the cereal grains, which are all closely related biogenetically. It is also of great importance that, in this instance as well as several others in my experience, the rash could be produced by the ingestion of Pablum Mixed Cereal. This contains wheat which has been cooked in the presence of moisture and therefore is presumably rendered less allergenic (7).



FIG. 14. (RGH 6945) Girl fourteen years of age. Chronic atopic dermatitis involving the cubital fossae.

Chronic atopic dermatitis of the flexural type in an older child is illustrated in Figure 14. The differential diagnosis between this condition and seborrheic dermatitis of the flexural type will be discussed subsequently.

ATOPIC ERYTHRODERMA

This term was invented by Hill (4) to describe a condition which represents perhaps the highest degree of atopic dermatitis in infancy. Hill observed this in 0.4 per cent of his cases. It is characterized by a generalized eruption, usually with some vesiculation, but more often

with periods of profuse scaling. The most distressing feature of this disease is the terrible persistent, severe, itching. Two distinct characteristics are: (1) blue, cold feet and (2) marked, general lymphadenopathy.

It has been found (6) that the histologic changes in the nodes are identical with those previously described by Hurwitt (5) under the name of "dermatophytic lymphadenitis" and found in lymph nodes removed from adults with chronic, non-specific skin diseases characterized by pruritis. The changes consist largely of fibrosis with some eosinophilic infiltration. In one instance in my practice an infant with very severe atopic erythroderma became seriously malnourished and developed a slate-gray color to her skin. I regarded



FIG. 15. (SMH) Atopic erythroderma in a six month old boy. Note the swelling in the left axilla caused by an enlarged lymph node.

this as "chronic atopic erythroderma." The child ultimately recovered. These infants are stubbornly resistant to all forms of treatment, dietary, environmental, and symptomatic. The antihistaminics give variable, but occasionally very gratifying, relief from itching but the beneficial effect of these drugs is commonly transient. It is in this particular condition that passive transfer tests were, and occasionally still are, invaluable guides to the infant's diet and environment. Experience with the use of ACTH and cortisone in such cases (4) has been very satisfactory in clearing the skin for direct testing and in the control of the pruritis. This method of treatment will be discussed in Chapter 17. Regardless of therapy, these infants usually improve, graduating into chronic atopic dermatitis.

An infant with atopic erythroderma is illustrated in Figure 15 which shows why the French pediatricians term these infants the "red babies." At the present time one would manage such a patient, if he proved, as in this case, refractory to the customary methods of treatment by clearing the skin at least temporarily with ACTH or cortisone. These drugs were not then available, but much very helpful information was obtained by passive transfer testing, and this particular patient eventually made a satisfactory recovery. During the course of hospitalization the child had two attacks of pneumonia. Without the use of sulfon compounds and antibiotics the infant would certainly have died and the death would then have been credited to ill-advised hospitalization of an eczematous infant.

ATOPIC DERMATITIS BY CONTACT

This condition is classified here rather than with contact dermatitis because the underlying sensitivity is that of the deeper layers of the skin (true cutis) as in atopic dermatitis rather than to hypersensitivity of the epidermis as in contact dermatitis. Hence, in this condition, the lesions are produced by the contact of highly sensitive skin to substances which typically act as allergens in other ways than by contact, as, for example by ingestion or inhalation. In such instances the allergens reaches the sensitized tissues by the method which Sulzberger (8) terms "transepidermal penetration." A common example of this is the child who is so highly sensitive to egg that he will develop a rash of an atopic character merely on handling eggshell. Other allergens as silk and wool, may also cause atopic dermatitis by contact in individuals highly sensitive to those substances.

The treatment of atopic dermatitis will be discussed in detail in Chapters 17, 18 and 19.

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IMPORTANCE OF INHALANT ALLERGENS IN ATOPIC DERMATITIS

LOUIS TUFT (7) has recently stimulated renewed interest in inhalant allergens (other than osmyls) as possible causes of atopic dermatitis. As long ago as 1918, Walker (8) reported two patients with eczema due to horse dander. He pointed out that when eczema is due to an inhalant allergen it is necessary for the physician to be extremely careful not to exceed the limit of tolerance of the patient as the eczema will be made worse. He also drew attention to the fact that if a patient has both eczema and asthma due to an inhalant, such as horse dander, that the doses of the allergen necessary to control the asthma under such circumstances are larger than those required to control the eczema and may aggravate the eczema. It is not the purpose of this chapter to review the literature of this subject as this may be found in Tuft's (7) report, except to briefly discuss the work of Osborne and Walker (4), my own work (2) not mentioned by Tuft, and the discussion by Diamond (1).

Osborne and Walker were of the opinion that in the etiologic study of eczema in infants and children, the first attack should be on the elimination of contact and environmental allergens. They concluded that water-soluble protein environmental allergens were absorbed at any point of contact. Moisture, especially perspiration, and friction are predisposing factors. Inhalation was believed to be important only in highly sensitized subjects. The allergen is then disseminated through the blood stream. They stressed the great importance of wool and point out that house dust contains a large amount of wool dust. In many instances exacerbation of the eczema can be demonstrated by having the patient wear a coarse sweater or gloves of this material.

Hill (3) studied the role of wool in considerable detail, and recommended patch tests as diagnostic aids. For this purpose the skin of the upper arm is gently scraped with a tongue depressor and a bit

of moistened white wool blanket applied as a patch test and left in place for a week. Positive reactions consist of erythema, fine crusted vesicles and papules. The usual methods for local treatment of atopic dermatitis are employed in wool sensitive cases and direct contact with wool is avoided. Where wool garments must be worn the skin should be protected from the wool by cotton clothing. Osborne and Murray (5) have also further emphasized the role of wool as a dominant allergenic factor in atopic dermatitis.

In severe cases hyposensitization with wool extract is advisable. Hill reiterates the advice originally given by Walker to the effect that in hyposensitization with an environmental allergen in atopic dermatitis it is always desirable to keep the dose low as these patients cannot commonly tolerate dosage that would be used in respiratory allergy.

In 1948 (2), I was impressed by the fact that the characteristic distribution of atopic dermatitis, in many instances with the lesions most pronounced on the face, the arms below the elbows and the legs below the knees (the exposed parts of the child's body), suggested a possible contact origin. It seemed reasonable to suspect that such lesions could be caused by a ubiquitous and powerful allergen, as house dust, which could conceivably act by contact, or by inhalation. It impressed me that if house dust does cause atopic dermatitis, positive reactions to patch tests should be obtained with house dust extract. Forty-two successive infants and young children with typical atopic dermatitis were given patch tests with concentrated pooled house dust extract. Both aqueous and lipid fractions were used, the latter since Stroud (6) had reported contact dermatitis in adults due to the lipid fraction of house dust. In this series there were three definitely positive reactions and three questionable reactions to the aqueous extracts. Four infants gave definitely positive reactions to dust lipid, and there was one questionable reaction to this extract. Only one patient reacted positively to both the aqueous and lipid preparations. In this instance good results were obtained after the injection of dust extract containing both fractions. However, since other measures were also being used, this one case proves nothing, and I did not feel it worth while to go further with this study. It is possible, however, that if I had applied the patches in the manner described above by Hill (3), and left them on for a week instead of

the customary forty-eight hours. I might have obtained more positive reactions. In the light of the studies discussed in this chapter it seems reasonable to suppose that the house dust acts as an inhalant allergen though this would not explain the distribution of the atopic dermatitis in the cases studied, unless one assumes that the action of the dust is through the blood, after inhalation, on skin previously rendered sensitive through long contact with the house dust.

The treatment of atopic dermatitis by the parenteral administration of extracts of inhalant allergens is carried out in exactly the same manner as hyposensitization with pollen or house dust.

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THE TREATMENT OF ATOPIC DERMATITIS

THIS may be considered under four main subdivisions:

1. Prophylactic.
2. Environmental control.
3. Symptomatic therapy:
 - a. Local.
 - b. Hormone therapy.
4. Specific therapy, dependent upon information obtained from:
 - a. History.
 - b. Skin tests, from which suggestions are obtained as regards environmental control, foods, and inhalant allergens.
 - c. Elimination diets.
 - d. Ingestion tests.
5. Psychosomatic: At times, possibly specific; at times, symptomatic.

The prophylaxis of atopic dermatitis and allergic disease in general will be discussed in Chapter 67. Environmental control should be instituted routinely in all cases. In addition to being a therapeutic measure for atopic dermatitis, it may also be considered as a prophylactic measure against the development of subsequent allergies, although proof that this is effective for this purpose is lacking. Environmental control consists chiefly in the avoidance of those allergens known to cause atopic dermatitis by contact or inhalation, such as wool, silk, soap, house dust, animal danders, etc. The parent should be given specific detailed information regarding the necessary procedures. I commonly use for this purpose the directions for environmental control noted in the addenda in the back of this book (Table XXX).

GENERAL MEASURES IN THE SYMPTOMATIC TREATMENT OF ATOPIC DERMATITIS

There are two fundamentals which must never be disregarded in the treatment of any allergic skin condition which will be discussed in detail. These are:

I. *LOCAL INFECTION MUST BE CLEARED*, if present, before any treatments directed specifically to the underlying skin condition are undertaken. Otherwise, the treatment is practically certain to end in failure. This was the case in the infant with impetigo complicating eczema illustrated in Fig. 17.

II. *BEFORE USING ANY NEW MEDICATION ON THE SKIN OF AN ALLERGIC INDIVIDUAL ALWAYS DO A PRELIMINARY "USE TEST."* If this is not done, unexpected and severe contact dermatitis will occasionally occur which may be a source of great suffering to the patient, as well as embarrassment to the physician.

I. TREATMENT OF LOCAL INFECTION

One of the best methods for clearing local infection is the use of effective, non-irritating antiseptic soaks. In infants and children boric acid should not be used for this purpose as this is not only a very inferior antiseptic, but deaths from boron poisoning have occurred (1).^{*} The best preparation for a local antiseptic soak is one of the quarternary ammonium compounds[†] in a dilution of 1/5000. These are non-toxic and in my experience have never caused contact dermatitis. The soaks should be applied for twenty to thirty minutes four times a day, after which the following modification of Rosen's ointment^{**} is used:

Zephiran chloride (12.8%) [‡]	1.00
Burow's solution	10.00
Hydrosorb (Abbott) [§]	20.00
Lassar's paste qs ad	60.00

This should not be confused with the use of 5 per cent borated talcum powder which is harmless when applied to the skin of normal infants.

^{*} Zephiran of the Winthrop Chemical Co., which is a mixture of high molecular alkylmethyl benzyl ammonium chlorides, may be used, or Phemerol, a similar preparation of the Parke, Davis Co.

^{**} The formula for Rosen's ointment was never published by Dr. Rosen—personal communication to the author from Dr. Isadore Rosen through the courtesy of Dr. Rudolf L. Baer. The formula for the original Rosen's ointment which, for obvious reasons, is also known as the 1-2-3 ointment, is:

Burow's solution	10.00
Anhydrous lanolin	20.00
Lassar's paste	30.00

[‡] This is the strongest solution in which Zephiran is commercially available.

[§] Hydrosorb (Abbott) is composed of fatty acid esters of diethanolamine in petrolatum U.S.P. (2).

The Zephiran in this ointment has been shown to have an inhibitory effect upon the staphylococci of the skin. Hydrosorb is substituted for the lanolin of the original Rosen formula because some patients who are sensitive to wool are also sensitive on contact to lanolin (5). Aqueous gentian violet, 2 per cent solution, as advocated by Ratner (3) for use in weeping atopic dermatitis, may also be used after soaking and before applying the above ointment.

Not infrequently, in order to heal locally infected areas, antibiotic ointments are used. Among these are aureomycin ointment (Lederle), bacitracin ointment (Bacidrin—Upjohn), or bacitracin plus tyrothrycin (Tyrotrace—Sharpe & Dohme). Neomycin ointment is also used, and new ointments of this character are appearing almost daily. Dermatologists tend to avoid the local application of penicillin, which is often the most effective preparation, because of the high incidence of sensitization in adults. Fortunately, this is very uncommon in pediatric practice where penicillin ointment and cream may be freely used if necessary but are probably best avoided because of the possibility of sensitization. Sulfon preparations are now rarely employed locally because of their high sensitization potential. The general principle is to avoid sensitization by local application to any drug it may eventually be desirable to use by mouth. If the skin infection does not clear on topical treatment, oral or parenteral therapy with sulfon or antibiotic drugs is indicated. This subject is further discussed in Chapter 20.

II. THE "USE TEST"

Although contact dermatitis from locally applied medication does not occur nearly as often in pediatric practice as in older age groups, nevertheless it does occur and may be very serious, as previously indicated. It is, therefore, highly advisable to be as sure as one can that any locally applied medication will not disagree with the patient. This information may be obtained by doing a "patch test" or a "use test," the latter being somewhat more practical. The following instructions should be given to the patient in writing, with a carbon copy on the office record:

"Before applying any new medication of any kind to the child's skin, always do a "Use Test" first. This is done by applying a small amount of the material to be tested to an area of affected skin the size of a nickel (2 cm. or 3/4 inch in diameter) four times during the

course of a day. If, by the next morning, the area where the medication was applied does not appear to have been irritated, the medication may now be used over the entire area to be treated."

Bathing

This is a very important part of the local treatment of the child with atopic dermatitis, and, if properly carried out, adds greatly to the comfort of the mother and child. Because tap water is hypotonic and the inflamed eczematous skin acts like a semipermeable membrane, it is necessary to decrease the osmotic pressure of the water with respect to the skin, and this is most satisfactorily done by the addition of colloids. The most satisfactory colloid baths are prepared as follows:

CORNSTARCH:* Stir up one or two cups in a tub of tepid water. Soak patient fifteen minutes. Dry by patting with an absorbent towel, not by rubbing.

OATMEAL: The most convenient preparation is Aveeno.† One cup (about 5½ oz. or 175 cc. by volume) is sifted carefully into lukewarm bath water to avoid lumping. This makes a highly satisfactory colloid bath, but is much more expensive than the other baths here described and care must be exercised because the bottom of the tub becomes very slippery. Cooked oatmeal may be used instead in the same manner as described for the bran bath below.

BRAN BATH: Prepare a cheesecloth containing one-half to one pound of wheat or oatmeal bran. In filling the tub, allow very hot water to run over and through the bag. Complete filling tub with water at a suitable temperature. Squeeze bag occasionally in water or use as a wash cloth.

Tar Baths

Certain tar solutions may be used with much benefit in the bath water, either with or without colloid. The preparations most commonly used for this purpose are:

LIQUOR PICIS CARBONIS (NF): Liquor carbonis deturgens. This is a saponified alcoholic extract of coal tar. Two cups full (twelve to sixteen oz.) are added to the tub of water. The patient is bathed for ten minutes. The room, water and towel should be at body temperature.

* Laundry Linit (Corn Products Co.) is satisfactory and inexpensive.

† E. Fougere & Co., Inc., 75 Varick Street, New York 13, New York.

ALMAY TAR BATH:* This is a thirty-five per cent solution of juniper tar (oil of cade) in propylene glycol, propylene glycol monostearate and water. Two to four tablespoons (thirty to sixty cc.) are added to a tub of water.

ZETAR EMULSION:† One to three tablespoons are dissolved in a tub of lukewarm water. Immerse up to one-half as tolerated.

Soap Substitutes

The majority of dermatologists feel that in most patients with atopic dermatitis the skin is aggravated by the use of soap. A soap is, by definition, a glycerol ester of a higher fatty acid. The exact mechanism by which soap may do harm in atopic dermatitis is not known. Sulzberger and Baer (4) suggest that soap, by virtue of its degreasing and keratolytic action, favors the percutaneous penetration of environmental allergens to which atopic patients are often highly sensitive. Therefore, soap substitutes are used.

The principal classes of soap substitutes are:

1. UNTREATED VEGETABLE OR MINERAL OILS: These are poor detergents, cleanse only mechanically and are unpleasant to use, particularly because of their greasy feel.

2. SULFONATED OILS: Sulfonation or sulfation is a term applied to a group of compounds arising from the action of sulfuric acid on oil or fat which is partially unsaturated. The characteristics of the final product depend upon the method and degree of sulfonation. The term "sulfonated oil" does not designate a definite clinical entity. Such oils as olive, cod liver oil, tea seed, and castor oil may be sulfonated. Acidolate** is a representative of this group of preparations. It consists of sulfonated olive and tea seed oils with liquid petrolatum and water. Sulfonated oils are more satisfactory than the untreated vegetable or mineral oils. However, they defat and dry the skin, do not make suds, and are unpleasant to use because of their greasy feel.

3. WETTING AGENTS: These are active detergents. They make suds, are pleasant to use, but they defat and may sensitize the skin, although this does not often occur in infants and young children.

* Almay Division, Schiefflin Co., 22 Cooper Square, New York 3, New York.

† Dermik Pharmacal Co., Inc., Brooklyn 12, N.Y.

** White Laboratories, Inc., 113 N. 13th St., Newark 7, N.J.

particularly if the clothing washed with these preparations is thoroughly rinsed. Drene, Dreft, and Vel belong in this category.

The most common soap substitutes used by the author are:

LOWILA CAKE:* This is composed of lauryl sulfoacetate in an inert diluent moulded into the shape of a cake of soap. This is particularly helpful because of the fact that it makes some suds, thus giving the mother the feeling that she is simply using another kind of soap.

PHISODERM:† This is a sudsing, emollient, detergent cream containing entsufon (sodium octylphenoxy ether sulfonate), lanolin crystals, lactic acid and petrolatum. This has the same pH value (5.5) as normal skin. It is supplied in three types: regular, for the average skin, oily, for dry skin, and a dry type for oily skin. This is an adequate substitute for liquid soap.

DERMOLATE:** This is superfatted soap which is often tolerated better than the more commonly used toilet soaps.

In the washing of the child's clothes it is important not to use soap because of the tendency for insoluble calcium salts to be formed and adhere to the cloth fibers. These may irritate the child's skin. A detergent such as Vel (Colgate) should be used and this should be thoroughly rinsed out of the clothing. If a child is sensitive to wool or silk the clothes should not be cleansed in the same water used for such materials.

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* Westwood Pharmaceuticals, 468 DeWitt St., Buffalo 13, N.Y.

† Winthrop-Stearns, Inc., 1450 Broadway, New York 18, N.Y.

** White Laboratories, Inc., 113 N. 13th St., Newark 7, N.J.

LOCAL TREATMENT OF ATOPIC DERMATITIS

THE LOCAL treatment of atopic dermatitis and the other eczematoid dermatoses is exceedingly important. A good dermatologist who is thoroughly familiar with the subject can often accomplish more than an otherwise competent physician or pediatric allergist who is not. It is important to avoid medications which sensitize the skin allergenically or which act as primary irritants on the skin. Gaul and Underwood (3) have emphasized the importance of avoiding over-care and over-treatment. They point out that a chemical injury to the skin from soap and water, oils and lotions, or over-care is the subthreshold groundwork for the stressing effects of the environment.

Because the patient with atopic dermatitis demands immediate relief, it is essential that the physician treating this disease should be thoroughly familiar with this phase of the treatment so that symptomatic relief may be given while the fundamental causes of the difficulty are being investigated. The number of preparations which may be applied locally is legion and is an eloquent testimonial to the effect that the perfect local treatment has not yet appeared. The physician, unless he is a dermatologist, cannot hope to make himself master of all methods of local treatment and will eventually select a few preparations which give the best results in his own hands. He will use some of the standard preparations learned in medical school, and others taken from standard text books of dermatology and allergy (see appendix to bibliography). He will try still others from reports on difficult cases which he has referred to dermatologists and allergists for consultation, and he will also try, in turn, the various samples from pharmaceutical houses that arrive daily at his desk in unending profusion. From among all these, as well as from some he will originate himself, the physician will eventually select the few that have given the best results in his own hands and

learn from experience the best way to use these in his own cases. Also, as Ratner (7) has pointed out, if one consults the United States Dispensatory (not to be confused with the U.S.P.) he will find listed practically every ointment in common use, and by a proper utilization of this information ointments can be created to fit the needs of the individual patients.

The nature of the medicament to be used for local application, assuming there is no infection (see page 109) and that "use" tests have been properly done (see page 110), will depend upon the relative *Acuteness* of the process.

WET DRESSINGS

For the acute, exudative stage, wet dressings are preferable. The most satisfactory preparation for this purpose is *Burow's solution* (solution Aluminum Acetate NF 1/10 or 1/20). This is most conveniently prepared by using the "Domeboro" tablets or powders.* A dilution corresponding to a 1/20 Burow's solution may be easily prepared by dissolving one of these tablets or powders in a pint of tap water. This dilution may be used upon any portion of the body, including the eyes and orifices. This is practically the only wet dressing used by the author on acutely inflamed skin.

Potassium permanganate solutions are useful on occasion and may be used in a 1/5000 to 1/10,000 dilution. One tablet of 0.13 gm. (2 gr.) dissolved in 130 cc. of water (4½ oz.) will make a 1/1000 solution. This preparation, while highly satisfactory, is also very messy.

Boric acid solutions are not used for reasons previously given.

APPLICATION OF WET DRESSINGS

Much of the effectiveness of wet dressings will be lost if they are not properly applied. The following instructions should be given:

1. Do not use cotton. The pack is best made with about twenty layers of cheesecloth, and should be somewhat larger than the area to be treated. The pack should be soaked in the solution and wrung out only to the point where it is not runny.

2. Waterproof material may be placed about the pack to pre-

*Dome Chemicals, Inc., 109 W. 64th Street, New York 25, New York.

vent soaking bedding or furniture. However, since evaporation is desirable, the entire pack should not be covered with waterproof material.

3. Every hour completely remove the pack, rewet by immersion and replace it. Pouring the solution over or under the pack is not satisfactory. If the pack becomes dry before an hour, rewet it sooner.

4. Fix the pack, preferably by overlapping and fastening with large safety pins or tie straps. Do not wrap it with bandage.

Ratner (7), pointing out the difficulty of applying wet dressings to the skin of patients in this age group, recommended painting the raw or oozing areas with two to four per cent aqueous solution of gentian violet medicinal over which calamine lotion, in single or double strength, with or without one per cent phenol, may be applied if desired. The gentian violet in such cases, as in burns, has a drying or "tanning" effect. Whenever gentian violet is used, be sure to warn the mother to be particularly careful of staining the clothing, bedding, and upholstery.

Not infrequently it will be found impossible to keep a wet pack on a child for more than twenty minutes at a time, and it is almost never possible, outside of a hospital, to keep wet dressings on at night. For these reasons, in the intervals where wet dressings are not kept applied, the 1-2-3 ointment of Rosen, with or without Zephiran (see Chapter 17), is the only preparation used by the author.

Other lotions which may be used in the acute exudative stage are:

1. Menthol ($\frac{1}{4}\%$)	0.6
Phenol (1%)	2.4
Ethyl aminobenzoate (Benzocaine) (5%)	12.0
Calamine lotion qs ad	240.0

Benzocaine may sensitize the skin so should not be used indefinitely.

2. Solution of aluminum acetate (15%)

Glycerin	aa	3.8
Purified talc		
Zinc oxide	aa	42.0
Lime water (fresh) qs ad		240.0

SUBACUTE AND CHRONIC ATOPIC DERMATITIS

After the acute stage of the eczema has subsided, local treatment consists largely in the application of various ointments. One characteristic feature of local treatment which is soon observed is that any new preparation may help very definitely for a time and then appear to lose its effect. The reasons for this are not known. It is, therefore, essential that the pediatrician have at his command a number of effective preparations which may be used in rotation while he is endeavoring to seek out the allergens causing the patient's difficulty. The best of these preparations contain tar, which, with the exception of hydrocortisone, is the single most effective medication employed in the treatment of atopic dermatitis.

TAR

Tar was doubtless first used as a folk medicine. It was probably first used in medicine in a pure form or painted on by Brocq (1) of Paris, and by Dind (2) in 1909. White (10), of Boston, learned of its use from them and, in 1916, was the first to introduce its use into dermatology in this country. The importance of tar in pediatric dermatology is such that it is felt advisable to discuss some of the more important characteristics of tar as described by Obermayer and Becker (6) in their comprehensive treatise.

It must first of all be understood that a tar is not a specific chemical compound. *Any substance obtained by the destructive distillation of organic material is a tar.* There are four main groups of such materials from which therapeutically useful tars may be obtained. These are:

1. WOOD TARS: The principal wood tars are:

Juniper—Oil of Cade (*Oleum cadini*).

Birch—*Oleum rusci*.

Pine—*Pix pini*.

The wood tars have an acid reaction and do not sensitize to light.

2. COAL TAR: The principal coal tar is *pix lithranthraxis* (*oleum lithranthraxis*) made from anthracite coal. This is the ordinary crude coal tar. Its chemical composition varies with the origin of the ma-

terial, the temperature at which the tar is produced and the quantity of the tar processed at one time. The smaller the retort, the more uniform are the batches of tar. Probably none of the constituents of coal tar exist in the coal. They are formed in the process of distillation.

Crude coal tar is characterized by the predominating occurrence of hydrocarbons: benzol, toluol, naphthalene, anthracene, and phenols. It is alkaline in reaction. For dermatological purposes only tar distilled at low temperatures should be used. Coal tar is anti-pruritic, antiacanthotic, vasoconstrictive, keratoplastic, and anti-parasitic.

Coal tar has a photosensitizing effect so that after its application the patient should not be exposed to sunlight, even through a window glass. If crude coal tar is applied to the skin for even fifteen minutes and then removed the skin may be sensitized to light (short rays of visible and long rays of ultraviolet) for as long as seventy-two hours afterwards.

Coal tar has a carcinogenic effect, but carcinoma as a result of the use of coal tar in infancy and childhood has never been reported.* *Coal tar is the only tar having a photosensitizing and carcinogenic effect.*

3. BITUMINOUS TARS: The most important tar in this group is *ichthyol*, which is obtained from bituminous formations containing fossil fish. It differs from coal and wood tars in that it contains about ten per cent sulfur, whereas the sulfur content of coal and wood tars is negligible.

4. PETROLEUM TARS: The principal tar in this group is naphthalan (same as naftalan).

All of the above tars are used in the treatment of atopic dermatitis. Occasionally a tar from one source will give a brilliant result after a tar from a different source has failed completely.

Figure 16 illustrates the importance of employing tars of various origins in atopic dermatitis. This patient was a nine-year-old girl with exceptionally severe chronic atopic dermatitis involving particularly the skin of the neck and of the lower legs. Because of its

* Personal experience of the author and personal communications from Dr. Marion B. Sulzberger and Dr. Maximilliam B. Obermayer.

severity and the fact that the skin failed to respond to all therapeutic measures commonly employed, a skin biopsy was made. This was examined by Dr. Charles S. Miller of the New York Post Graduate Hospital who confirmed the diagnosis of chronic atopic dermatitis. Dr. Albert R. McFarland, who saw the child in con-



FIG. 16. Chronic atopic dermatitis in a nine year old girl. The only therapeutic measure of any value in this patient was pine tar.

sultation, went over the patient's record very carefully and noted that wood tar had never been applied. He suggested its use and the patient responded dramatically. This happened not only on that one occasion but on many occasions afterwards. Needless to say, since that experience the use of wood tar in eczema which has failed to respond to coal tar has been routine in my practice.

WHITE TARS

Because of the disagreeable appearance of crude coal tar, attempts have been made to extract the active principles of the tar as regards eczema for use in an ointment base. Nelson and Osterberg (5) extracted the steam distillate of crude coal tar with ether and obtained a product which they felt was as efficient as crude coal tar but was almost white. This extract is commonly used in

five and ten per cent strength in ointments and may be obtained as proprietary preparations under the names of Taralba (Upjohn), Taroxide (Abbott), and Supertah (Talby-Nason).

Dr. Samuel W. Clausen* obtained a highly satisfactory "white tar" by the extraction of crude coal tar with hot alcohol. Irritating material is removed by low pressure distillation. This preparation is commonly used in three per cent strength in an ointment base. It is not as yet commercially available.

LASSAR'S PASTE

This is one of the most commonly used ointment bases and is a National Formulary preparation (Pasta Zinci oxide 1942; paste zinc oxide or Lassar's plain zinc paste). In most prescriptions, the word "plain" is omitted. This is made up as follows:

Zinc oxide	25%	
Starch (corn or arrowroot)	25%	aa 15.0
White petrolatum	50%	qs ad 60.0

Lassar's paste is a good vehicle for:

Ammoniated mercury	2%
Crude coal tar	2-5%
Tar extract (Clausen)	3
Phenol	1/4-1
Salicylic acid	1-5 (depending upon whether a stimulating or keratolytic action is desired)

It is important that Lassar's paste should not be thickly applied to a weeping area and left without frequent examination of the skin as, under such conditions, crusts may form and the skin become secondarily infected with serious results. Such a case was reported by White (12).

For most purposes, the author favors the use of 3 per cent Clausen tar extract or 2 per cent crude coal tar in Lassar's paste. It is also, occasionally, very much worth while, as stated above, to substitute a wood tar, such as juniper tar (oil of cade), or a bituminous tar (ichthyol), if the coal tar is not effective, as occasionally

* Unpublished data.

an amazingly good response may be obtained from one type of tar when another type has failed.

Crude coal tar alone is often very satisfactory. It should be painted on and allowed to come off by itself. After application, it may be covered with powdered starch. It is highly important to be sure that this is not applied over infected skin.

Compound resorcin ointment (NF) is especially favored by Robinson (8). It should be smooth and moist when dispensed. Its formula is:

Resorcinol	
Zinc oxide	
Bismuth subnitrate	aa 6.0
Juniper tar	2.0
Yellow wax	10.0
Petrolatum	29.0
Wool fat (lanolin)	28.0
Glycerin	13.0
	<hr/>
	100.0

Vioform* (iodochlorhydroxyquinolene), discussed subsequently under seborrheic dermatitis (page 151), is sometimes useful for atopic dermatitis. It may be used alone or with tar:

Vioform (Ciba) (2%)	
Crude coal tar	aa 1.2
Lassar's paste qs ad	60.0

Pragmatar,† which is acetyl alcohol coal tar distillate 4 per cent, near colloidal sulfur 3 per cent, and salicylic acid 3 per cent in an oil-in-water type emulsion base, while particularly useful in seborrheic dermatitis, is also sometimes helpful in atopic dermatitis.

Hill** has reported good results in the treatment of stubborn

* Ciba Pharmaceutical Products, Inc., 556 Morris Avenue, Summit, N. J. Vioform may be prescribed as a powder for use in ointments, or vioform ointment, or a cream, as prepared by Ciba, is now on the market in 3 per cent strength. The former is in a petrolatum and the latter in a water soluble base.

† Smith, Klein and French.

** Personal communication to the author slightly modified from that described in reference (11).

patches of chronic atopic dermatitis with the Swartz (11) ointment. The formula for this is:

Mercurochrome crystals (4%)	2.4	
Salicylic acid (6%)	3.6	
Water qs to dissolve		Sig: Rub in well
Anhydrous wool fat		twice a day and
Petrolatum aa qs ad	60.0	bandage on.

The above is a very messy preparation and the mother should be warned concerning the staining of her linens, upholstery, etc. with mercurochrome.

There are many proprietary preparations which will occasionally be found useful. One of the best known of these is Mazon.* Its exact composition is not known, but according to a recent label it contains sodium stearate, benzoic acid, salicylic acid, tars and mercury salicylate (0.06 per cent) in a vanishing cream base. It must not be used in patients sensitive by contact to mercury. This will, of course, be discovered if a "use test" is done.

Sulzberger *et al.* (9) early reported good results with the use of hydrocortisone acetate ointment locally in the treatment of atopic dermatitis. Subsequent experience has shown that this is the most effective local treatment now available and when these preparations become less expensive it is quite likely that this or subsequently developed steroid preparations will be those of choice in the local treatment of atopic dermatitis. The strengths most commonly used are 1 per cent and 2.5 per cent. Occasionally it is desirable to add an antibiotic to the preparations.

On rare occasions a course of Fowler's solution (liquor potassii arsenitis, U.S.P.) administered in the orthodox manner, with the dose according to age of the patient, may result in dramatic improvement. However, as when any other arsenical is administered, the patient must be very carefully watched for evidence of arsenic intoxication.

According to MacKee and Cipollaro (4) roentgen rays are exceedingly efficacious for eczematoid eruptions of almost any type, but the improvement is often only temporary. They are employed occasionally in the treatment of children and rarely in infants. Grenz rays are safer but less effective and may be used for small patches.

* Belmont Laboratories, Philadelphia, Pennsylvania.

Ultraviolet radiation may be helpful for certain types. In my own practice these forms of treatment are now almost never used.

The fact that atopic dermatitis will occasionally clear in the presence of acute intercurrent febrile infections (see Chap. 14) has led to attempts to relieve this condition by means of artificially induced fever. This method of treatment has never attained any degree of popularity and in my experience the slight and transient relief obtained by this form of therapy has been considerably out of proportion to the trouble and discomfort involved in carrying it out.

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CHAPTER 19

THE TREATMENT OF ATOPIC DERMATITIS WITH CORTICOTROPIN (ACTH) AND CORTISONE*

THE INDICATIONS for the use of ACTH and cortisone in the treatment of atopic dermatitis are stated as follows by Baer and Leider (2):

1. To control severe exacerbations of a relatively otherwise stationary eruption.

2. To permit orthodox forms of therapy to become more effective. This refers to those severe cases of atopic dermatitis in which the patient cannot obtain relief from any of the accepted forms of therapy, i.e., while the patient is in a state which is in some ways similar to status asthmaticus. When ACTH or cortisone is administered in such cases, even if they do not completely control the eruption and itching, some patients again respond to topical medication and systemic antipruritic therapy.

3. While ACTH and cortisone should not as a rule be used in atopic dermatitis over long periods of time, there are some otherwise intractable cases in which very small maintenance doses (e.g., cortisone 25 mg. daily) are adequate to control the eruption and itching. In such exceptional cases it seems warranted to continue the medication over protracted periods of time. I have as yet been able to do this in eczema with children in only a few cases as the drugs had to be discontinued eventually because of the development of adiposity and other evidences of hyperpituitarism.

To the above three indications I should like to add one more:

4. These drugs may be used, at least temporarily, to clear an eczematous skin for direct testing. This is particularly valuable in infants with atopic erythroderma and other patients where the skin

* In conjunction with this section, the reader is advised to study the general discussion of ACTH and cortisone in Chapter 39.

is so generally involved that the only other satisfactory way of testing would be by means of passive transfer. In every instance where ACTH or cortisone has been used to clear the skin, the results of direct testing have confirmed tests previously made by the method of passive transfer (3). I do not agree with those who state that skins which are more or less chronically eczematized give completely unreliable results on direct testing. Skin tests are far from being completely reliable under any circumstances and the involvement of skin more or less in the eczematous process does not add appreciably to the degree of unreliability. I have not found that ACTH or cortisone significantly affects the results of skin testing. This also has been the experience of Andersson (1).

In the treatment of atopic dermatitis in infancy and childhood I prefer ACTH to cortisone for reasons to be discussed (see Chap. 39). The dose of the ACTH is 10 to 20 units of the aqueous preparation every six hours, or twice as much of the slowly absorbable preparation every twenty-four hours. As soon as the patient starts to improve, usually eight to twenty-four hours, the dose is gradually reduced and the interval gradually increased until a maintenance dose is found. It is preferable to start with larger rather than smaller doses and gradually decrease rather than increase to satisfactory therapeutic levels.

The dosage of cortisone has been studied by Hill (4) who prefers to start with 75 mg. orally daily. This, in my experience, is best given in divided doses of 25 mg. every eight hours by the clock. Occasionally a patient will be found who requires somewhat larger doses, but this does not happen very frequently. Hill notes that, while infants may require relatively large doses in proportion to their body weight, the severity of the disease is not the sole criterion of dosage. This may be perhaps because in many instances of atopic dermatitis the picture is confused by seborrheic elements which do not respond as well to cortisone therapy. The smallest dose of ACTH or cortisone that will keep the patient under control along with the usual symptomatic remedies should be considered the optimum since it may be necessary to keep the patient under therapy for many months. During this time the search for the underlying etiological causes must be carried on because these drugs, for the most part, offer symptomatic therapy and not cure. Both ACTH and cortisone

should not be withdrawn abruptly, but gradually tapered off. Lever (5) stated that the rebound of the disease, after discontinuing therapy, is worse than in most other diseases. This has not been my experience. While on hormone therapy it is necessary to follow the precautions discussed in Chapter 39.

O'Keefe (6) has advised the use of oral cortisone just to the point where the skin is not completely cleared. In this way the effect of foods, other allergens and various forms of treatments will not be masked. It is my custom to do this and also to use ACTH in the same manner.

Cortisone ointment has no value in the treatment of atopic dermatitis (3). Hydrocortisone ointment has a very markedly beneficial effect as has been mentioned previously (7).

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COMPLICATIONS OF ATOPIC DERMATITIS

I. IMPETIGO

THE MOST common complication of atopic dermatitis is impetigo (Fig. 17). It is ordinarily caused by a staphylococcus or a streptococcus. Usually, in the more stubborn cases, it is of the hemolytic variety. As discussed under the local treatment of eczema, *the in-*



Courtesy Jerome Glaser, M.D.,
from the Department
of Photography of the
Rochester General Hospital,
Rochester, New York.

FIG. 17. Impetigo complicating atopic dermatitis in a five months old girl.

fection must be cleared before specific local measures are used on the skin. Crusts should first be soaked off as far as possible, by the use of Burow's solution, in the manner directed for the treatment of crusted eczema. While penicillin ointment is probably the most effective single local measure, and although infants and children do not appear to be sensitized to any significant degree by its use, the

ointment is not employed on theoretical grounds unless all other measures fail. The use of aqueous aureomycin or neomycin solution, as recommended by Osborne (17), is highly effective. The solution is prepared by dissolving 50 mg. of either drug in 2 to 8 oz. of water, and using as a soak every four hours as often as necessary. It is claimed that sensitization to these drugs, when used as aqueous solutions, unlike when used in ointment form, does not occur. There are now available, if an ointment is desired, many antibiotic preparations, besides penicillin, which are very satisfactory. It is also occasionally necessary to employ oral or parenteral penicillin, or oral sulfonamides, or both, in very stubborn cases. In the less severe instances Vioform ointment (18, 24, 25) has been proven to be of considerable value.

ECZEMA VACCINATUM

Next to impetigo, probably the most common complication of eczema is vaccinia. Hershey and Smith (12), in 1945, reviewing the studies of Jubb (13), stated that the incidence of generalized vaccinia as a complication of smallpox vaccination varies between one in 20,000 to one in 96,000, and the case fatality rate between 12 and 30 per cent. About two-thirds of the patients in whom this complication occurs have diseases of the skin and many are children with eczema. The reason why generalized vaccinia occurs as a complication of atopic dermatitis is explained by the investigations of Gins and associates (9). In 1929, they demonstrated the vaccine virus in the mucus of the nasopharynx of children on the fourth and fifth days after vaccination. The work of Wollnitz (27), in 1938, who recovered vaccine virus from the urine of vaccinated individuals, was further evidence that this virus circulates in the blood for at least five days after the primary vaccination.

It has long been a common experience of clinicians that this blood-borne virus tends to localize in areas of previously damaged skin. For this reason persons with eczema are particularly likely to develop generalized vaccinia. While the introduction of the sulfonamides and the antibiotics has reduced the fatality rate in this disease to almost insignificant proportions, yet it is important that children and others should not be vaccinated against smallpox until the skin is clear. While not now commonly fatal, generalized vaccinia may

produce marked disfiguration of the skin through scar formation. Encephalitis, though an infrequent complication, is always very serious when it does occur. Furthermore, because the vaccine virus can be spread to eczematous skin by direct contact with a reacting vaccination, or indirect contact through towels, etc. it is important not to vaccinate children in a home where there are children with eczema who have not been previously vaccinated. I have seen patients with large scars on their cheeks resulting from vaccinia contracted thru eczema of the face because of sleeping with a recently vaccinated sibling. I also know of one unvaccinated infant with generalized atopic dermatitis who died from generalized vaccinia after a bath in a tub just previously used to wash an infant with a reacting vaccination.

In case of accidental exposure to vaccine virus it is possible that the early administration of human immune globulin might abort or modify the course of the infection (28). Probably, fairly large doses as 20 or 30 cc. should be used. Transfusion from a previously successfully vaccinated donor should be considered if immune globulin is not available.

Allergic reactions following vaccination are apparently quite rare. I have several times seen urticaria, which I have classified as infectious urticaria secondary to vaccination. According to Curth and associates (4) anaphylactic reactions to vaccine virus have not been proven. They have reported papular eruptions, erythemas, and erythema multiforme, occurring as a complication of smallpox vaccination, and probably represent allergic reactions to that procedure.

ECZEMA HERPETICUM—KAPOSI'S VARICELLIFORM ERUPTION

In 1887, Kaposi (14) described a rare type of eruption occurring as a complication of infantile eczema. He saw ten cases of this varicella-like eruption which had not been previously described and called it "eczema herpetiforme." However, the term now in common use to describe this condition is the eponym, "Kaposi's varicelliform eruption." This disease nearly always represents a hematogenous infection with a virus which localizes in the skin and nearly always in some area where the skin has been damaged by disease of one type or another. Barton and Brunsting (1), in 1944, thoroughly re-

viewed the literature of this subject and stated that atopic dermatitis was present in 80 per cent of the cases, and in 70 per cent, the patients were children under four years of age. The most common virus to cause this disease is the virus of vaccinia, as previously discussed, and when the disease is known to have been caused by this virus it may then be specifically termed "eczema vaccinatum." However, we now know that other viruses, and particularly the virus of herpes simplex, may cause a disease having an identical clinical appearance and course, and be indistinguishable from that caused by the virus of vaccinia except by the history and by laboratory tests for identification of the virus.

In 1944, Wenner (26) described three cases of Kaposi's varicelliform eruption in infants, two girls of five and eight months, respectively, and a boy of twenty months. The disease was characterized by an eruption which passed through the stages of papule, vesicle, pustule and crust. The lesions appeared in crops, had a transitional course lasting seven to ten days, and in two of the infants spread by confluence to attack large areas of the skin. Generalized herpes simplex occurring in an intact skin is exceedingly rare. Finberg and Easton (7) described such a case in a seven year old girl with meningococcemia and stated that they were able to find only two other instances in the literature where this disease, in an intact skin, might possibly have occurred. During the first week of Wenner's cases, new vesicles, which quickly became purulent, appeared, scattered among the older pustules. The mucous membrane of the mouth was a seat of small, reddened ecchymotic lesions up to 2 mm. in diameter. There was fever and a relative leukopenia. One infant died with symptoms of encephalitis, but this diagnosis could not be confirmed by a necropsy. The chief differential diagnosis would appear to be from eczema vaccinatum. However, from all three of Wenner's cases a virus similar to, if not identical with, the virus of herpes simplex was isolated.

Lynch (15), in reporting a number of these children, pointed out that the eruption originally termed "eczema herpetiforme" by Kaposi, because it resembles herpes simplex, actually is herpes simplex in an extensive form. Hence, this disease should be called "eczema herpeticum" or spoken of as extensive herpes simplex complicating eczema (or other dermatoses).

Ruchman, Welsh, and Dodd (20) have reported four cases of

Kaposi's varicelliform eruption in patients with atopic dermatitis. Three occurred in adults and one of these was fatal. One occurred in an infant fourteen months of age. In all instances, there was a definitely known exposure to herpes simplex five to ten days before the onset of the eruption and no history of exposure to vaccinia virus. The virus of herpes simplex was isolated from the cutaneous lesions of all four patients. The lesson to be learned from this is: parents who have herpes simplex should avoid contamination of the skin of their eczematous children with saliva, if the herpes happens to be in or about the mouth, which is commonly the case with the milder forms. It is also within the realm of possibility that other viruses, such as those of chicken pox, for example, may possibly cause this disease. However, this appears unlikely because both chicken pox and atopic dermatitis are very common disorders and if Kaposi's varicelliform eruption were due to the virus of chicken pox one would expect a much higher incidence of the disease.

OTHER INFECTIONS COMPLICATING ECZEMA

The emphasis on Kaposi's varicelliform eruption (eczema herpeticum) has recently tended to overshadow the fact that eczema may be complicated by infections which are not of virus origin. In this connection, the communication of Boisvert and Powers (2) is significant. These authors pointed out that atopic dermatitis and streptococcal fever, rhinopharyngitis, cervical adenitis, and low grade fever of several weeks duration) are common diseases in the same period of life, the first three years. In thirty-nine cases of secondarily infected eczema, hemolytic streptococci were recovered from twenty-six (66%). From this small series it would appear that hemolytic streptococci are associated with infected eczema in about two-thirds of the cases. Of thirty-six clinically infected, hospitalized patients, whose skin culture showed hemolytic streptococci, twenty-nine (77%) also carried that organism in their rhinopharynx. Blood cultures were positive for hemolytic streptococci in three of the thirty-six cases of clinically infected eczema with skin cultures positive for that organism. It would appear, therefore, that eczema in a child who has streptococcal fever, or who is a carrier of hemolytic streptococci, is likely to become infected.

Clinical differentiation between infected and non-infected eczema is not clear-cut. Weeping, according to these authors, is perhaps the

most important single differential characteristic suggesting that eczema is infected. However, I would not feel that weeping invariably indicated infection. Adenopathy, commonly present in eczema, is more marked when infection is present. Regardless of infection, a leukocytosis and an eosinophilia are often present in patients with eczema and are of little differential importance. Clearing of infection is usually ameliorative but not curative of the eczema. The infection, though not chronic, tends to recur because it is usually a part of the streptococcal fever, a sub-chronic ailment.

DeForest and Kerr (5) have described an interesting reversal of the usual course of events. An infant with infected eczema caused an epidemic of streptococcal infection in a group of nurses working on a pediatric floor rather than the infant's contracting the infection from a nurse. The patient described was a boy two years of age admitted with a generalized, fiery red eczema with a left purulent otitis media. Group A, type 14 hemolytic streptococcus was recovered from the skin. Later, the same organism was recovered from a nose and throat culture. During a three month period, seventy-four nurses took care of this child, and half of them developed streptococcal infections, about evenly divided between sore throats and scarlet fever. The parents and relatives who had taken care of the child previous to admission had also developed various infections, presumably of streptococcus origin. This case illustrates the high degree of communicability which hemolytic streptococcal infection in infancy may acquire.

Sulzberger and Baer (23), commenting upon this report, stated that in their extensive experience with severe, continually scratched and traumatized atopic dermatitis, they have not seen a single instance of severe invasive infection with staphylococci or streptococci. Four cases of erysipelas complicating atopic dermatitis in infancy were reported by Glaser and Edwards (11), but the comment of Sulzberger and Baer is essentially correct. While eczematous children not infrequently develop complications caused by cocci, they are nearly always infections of the respiratory or gastrointestinal tract, and the portal of entry does not appear to be the skin. The probable explanation is that the same reactive properties of the skin which result in atopic dermatitis also enable the skin to react effectively against the common skin organisms.

MISCELLANEOUS COMPLICATIONS OF ATOPIC DERMATITIS

RESPIRATORY AND GASTROINTESTINAL

Schwartz (21), in 1934, reported that respiratory complications and diarrhea are the most common complications of infantile eczema. These are much more frequent than complications involving the skin. These observations were corroborated by Glaser and Edwards (11), in 1940, to whom reference is made for detailed tabulation of the incidence of the various complications of atopic dermatitis.

RENAL DISEASE

Burke and Ross (3) in discussing acute glomerulonephritis in children in a series of ninety cases, found that the most common predisposing infections were those of the upper respiratory tract, a history of which was obtained in 65.3% of cases. Skin infections such as secondarily infected burns, impetigo and infected eczema, formed the next largest group of preceding infections, or 10.2%. Steiner (22) reported glomerulonephritis as a complication of atopic dermatitis in seven out of forty-one adults. Feuchter (6), in reviewing the literature of glomerulonephritis following infections of the skin with particular reference to the impetigo-nephritis syndrome, more common in children because impetigo is more common at that age, stated that doubtless many cases of impetigo are actually cases of pyoderma complicating other conditions such as eczema. However, in the series of infants studied by Glaser and Edwards (11), all of whom were hospitalized because of severe atopic dermatitis, nephritis did not occur. I believe that this is important evidence of how efficiently the skin with atopic dermatitis resists the invasion of bacteria and the absorption of their products. One child in another series (10) did develop nephrosis while under treatment for eczema with ACTH but this was believed to be coincidence.*

* Through the courtesy of Dr. Mitchell L. Rubin of the Buffalo Children's Hospital I have recently been provided with abstracts of the histories of a boy thirteen years, and girl seventeen months of age, both of whom suffered from atopic dermatitis complicated by acute glomerulonephritis. While there are doubtless other unreported cases, acute glomerulonephritis must nevertheless be regarded as a very uncommon complication of atopic dermatitis in children.

PYREXIA

Morse (16), in 1908, commenting upon the causes of obscure fever in infancy, stated that eczema is often accompanied by fever of long duration, presumably due to absorption of toxic products from the skin. Morse's observations are contrary to my own experience, probably because we can now treat infections causing fever much more effectively. Poulton (19) reported an infant with eczema whose fever accompanying what was apparently an acute respiratory infection rose to 110° r. The child recovered under modern therapy. Almost certainly, before this era, the child would have died and this would have been classified in the group of the mysterious "eczema deaths."

PHENYLPYRUVIC OLIGOPHRENIA

This rather infrequent disease, which is also termed phenylpyruvic ketonuria, while not a complication of atopic dermatitis, is of interest in this connection because these children have a marked susceptibility to atopic dermatitis. It is a form of congenital idiocy first described by the Danish chemist, Følling (8), in 1934 and should always be suspected in idiocy of unknown origin, especially if accompanied by eczema. Its incidence in institutions for the feeble-minded is approximately 0.8%. It is characterized, in addition to idiocy, by a variety of neurological stigmata commonly including athetosis. These children are often fair, well developed and attractive. The disease is associated with a primary metabolic defect resulting in the excretion of phenylpyruvic acid in the urine as a result of the incomplete oxidation of the amino acid, phenylalanine. This acid may be detected by the development of a transient but characteristic green color upon the addition of 5% ferric chloride to acidified fresh urine. Phenylpyruvic acid has never been demonstrated in the urine of a normal person. Phenylpyruvic oligophrenia is not amenable to treatment, is inherited, and is determined by a single autosomal recessive gene. The parents of the children with this disease should have no more children; neither should those afflicted or their immediate relatives.

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SUDDEN DEATH IN ATOPIC DERMATITIS

IT IS QUITE difficult, at the present time, when the death rate from infection has dropped so markedly because of the advent of modern chemo- and anti-biotic therapy, to realize with what misgivings the physician practicing prior to this era hospitalized patients with infantile eczema. It was notorious that these children commonly did very poorly and many of them died very suddenly from apparently unknown causes ordinarily not too long after hospitalization. These sudden, mysterious so-called "eczema deaths" practically never occurred outside of hospitals, and the cause of these deaths in hospitals, which we now believe to have been due to peracute infections, was not then known. Sulzberger, in 1944 (6), expressed the opinion that phenol poisoning from tar, in combination with interference with cutaneous respiration and the instability of the autonomic nervous system, would explain satisfactorily the symptoms as well as the other circumstances of some of the acute deaths from eczema. However, these deaths no longer occur, since the advent of modern methods of treating acute infections. Also, since we use tar as freely as before in the treatment of these children, I feel that Sulzberger's theory has been invalidated by the progress of events.

Schwartz (5), in 1934, reviewed the literature of this subject beginning in 1902 when Feer (3) considered the thymus gland as the responsible factor for sudden death in eczematous infants. Hutinel and Rivet (4) were the first to call attention to the factor of septicemia as the possible etiology. They regarded the hospital milieu as an unfavorable background for these infants with a diminished defense mechanism. Schwartz reported ten cases of infants with eczema who died following admission for treatment of this disease. Four had septicemia; four others a fulminating type of bronchopneumonia; and two died with intestinal intoxication. Whatever the complication causing death, the infants were uniformly very toxic during the last illness. This toxemia was usually associated with rapid weight loss

and dehydration. In a few, a sudden collapse was almost the only clinical evidence preceding the disastrous result. Schwartz called attention to the mysterious blanching of the skin, which sometimes occurs prior to death in these infants, which has brought about the lay tradition that it is dangerous to "drive-in" the eruption. While Schwartz stated that the significance of this remains as obscure today as when it was first commented upon three centuries ago, I believe that in the light of our present knowledge we may now attribute it to severe peripheral circulatory failure which may accompany acute sepsis in infancy and childhood.

Davies, in 1940 (2), could find a report of only one infant with eczema who died suddenly at home. This was a boy thirteen and one-half months of age, reported by Bernheim-Karrer (1), who had not acted very well for a week. At necropsy myocarditis was reported. Davies also reported three successive sudden deaths in his own experience of hospitalized eczematous infants.

I believe it is fair to state that we may now regard this era as happily past. Further evidence that this is true will be given in the next chapter.

It is worthwhile to bear in mind that if a person dies in what is suspected of being allergic shock, it is advisable to draw blood from the heart as soon as possible after death. If this is done, passive transfer studies can then be made, as discussed by Lund and Hunt (7) in an effort to discover the offending allergen.

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HOSPITAL MORBIDITY AND MORTALITY OF ATOPIC DERMATITIS

DESPITE the previously discussed long and unfavorable record of mortality and morbidity in hospitalized eczematous infants, no systematic studies of this subject were made until Koch and Schwartz (4) investigated the problem as it occurred in 103 patients with infantile eczema admitted to the Milwaukee Children's Hospital from August 1922 to April 1931. Their conclusions appeared to substantiate the previous unfavorable experiences and impressions recorded in the literature. In a series of fifty-six infants admitted for the treatment of uncomplicated infantile eczema the mortality rate was 17.9% which, as they pointed out, was higher than the then current surgical mortality rates reported by Cutler (1) for acute appendicitis of 11.4% ; empyema 16.4% ; pyloric stenosis 11.1% and fracture of the skull, 10.2%.

I had the impression, however, that our experience in Rochester was somewhat more favorable and, together with Edwards (3), studied all eczematous infants up to two years of age admitted to the Strong Memorial, Rochester Municipal and Genesee Hospitals of Rochester, New York, from January 1927 through August 1939. The mortality rate for the entire Rochester series of all these children was 3.8% , about one-quarter of the similar series in Milwaukee. The morbidity rate for the Rochester series was 20% which was just about one-third that of the Milwaukee series of 58.9% . Differences between the results of the Rochester series and the Milwaukee series cannot be explained by the introduction of sulfonamide drugs as at that particular time they had not come into general use. We had no explanation to offer for the marked contrast in the two series.

In 1943, Schwartzman, Dragutsky and Rook (7) reported a series of 128 healthy children (boarders) who were hospitalized for reasons totally unrelated to their health. One hundred and eleven were under two years of age. In the group under two years of age morbidity

occurred in 6.36% of cases, mostly upper respiratory infections. There was no mortality, and in the group over two years there was no morbidity. This morbidity of 6.3% in boarders under two years of age contrasted strikingly with the morbidity of almost 60% of infants admitted to the same hospital because of infantile eczema. This later figure is very close to the morbidity reported above for Milwaukee but almost three times the morbidity reported from Rochester.

The marked contrast in the morbidity and mortality figures between the true boarders and the eczemas in the hospital indicated that, although the true boarder was exposed to dangers and was susceptible, he was not as vulnerable to infection as the child with eczema, whose resistance was apparently impaired. This confirms the impression that the condition of the skin plays an important role in resistance to gastrointestinal and respiratory infection. Epstein (2), however, expressed the interesting and reasonable opinion, in which I concur, that these complications occur as the result of subclinical gastrointestinal and respiratory allergy. Schwartzman and associates concluded that no healthy children should needlessly be admitted to a hospital and particularly children with eczema or any other skin condition that could be treated outside. Epstein (2) was the first dermatologist to report on this subject, and was also the first physician to report on hospitalization of eczematous infants after the beginning of the sulfon era. He reported a series of 100 consecutive hospitalized cases of eczematoid dermatoses up to two years of age without deaths. Sixty-four of the infants were admitted with uncomplicated eczema. Of these, fifteen, or 23.4%, developed complications. All these infants, except one, had atopic dermatitis. The other infants of the series who had seborrheic dermatitis, contact dermatitis, and infectious eczema, chiefly intertrigo, developed no complications. Epstein stated that the morbidity in the atopic dermatitis infants indicates that there is a fundamental difference between these infants and the infants with the other types of eczematoid dermatoses.

Kaposi's varicelliform eruption occurred as an admission complication in three cases. All survived. One patient developed a paralysis of one foot which was considered by the attending pediatrician to be possible evidence of poliomyelitis. Epstein felt, however, that in

view of the fact that the virus of herpes simplex is a neurotrophic virus, the possibility exists that the paralysis might have been a consequence of that infection.

A much higher degree of eosinophilia was noted in atopic dermatitis as compared with nonatopic dermatitis. The average degree of eosinophilia was 9.7% which was about twice as high as in nonatopic dermatitis and about ten times as high as in the other skin conditions used as controls. Anemia, however, was found just as often in eczematoid dermatoses, as in the other dermatoses of children.

The mortality of zero in the author's series is explained chiefly by the use of sulfonamides when indicated and by excellent nursing care. Epstein felt that since the advent of sulfonamides death from eczema appears to have become an avoidable complication.

In 1947, Schwartzman (6) again made a study similar to that previously reported by him and associates (7). In this later review there were thirty-eight cases of eczema admitted without complications. Of these 65.8% contracted cross infections and 2.6% died. This represents one death which was an infant under two years of age. Of the thirty-three eczema patients admitted with complications 45.4% contracted additional infections and 6% (two patients) died, both infants under two years of age.

The morbidity for the fifty-two infants with eczema was 56.3% and the mortality 4.2%. This was a definite increase over the morbidity and mortality over the years 1934 to 1942, where there was a morbidity of 48.8% and a mortality of 2.3%. The author suggested the great scarcity of experienced help in the hospitals during the war period as a possible explanation for this increase in mortality and morbidity. In 1950, Schwartz (5) again reviewed the Milwaukee experience with eczema. Since his report (4) in 1935, in the same hospital there was but one death (0.3%) among 300 infants under fifteen months of age hospitalized because of eczema. This death was due to septicemia complicating otitis and a peritonsillar abscess. A spot check showed that only 40% of the infants in this later group had received antibiotic therapy. The suggestion was advanced that perhaps the marked reduction in mortality may have been due to reduction in the infectivity of the hospital environment induced by the use of antibiotics in those with active infections.

In concluding this chapter I feel that it is safe to state that we no

longer fear to admit infants with atopic dermatitis to the hospital providing that conditions are such that the infants will receive reasonable care.

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SEBORRHEIC DERMATITIS

THIS is the *most common* dermatitis in infancy. It occurs so often over the anterior fontanel in the form of the so-called "cradle cap" or "milk crust" that it may almost be considered physiological. Perhaps it occurs particularly in this area of the scalp because most mothers are timid about cleaning this "soft spot" vigorously and thus the scales accumulate and cause further irritation and spread of the condition.

The disease has been suspected of being of infectious origin, possibly caused by the *pityrosporon ovale*, presumably in combination with other organisms but this has never been proven and the etiology of seborrheic dermatitis is unknown.

For a discussion of the various theories reference is made to the review by Gans (1). In older children and adults "dandruff" represents the most common form of seborrheic dermatitis. It is probably the most common cause of alopecia and should therefore be treated early. Severe types of the disease are exudative, crusted and sometimes pustular. Severe seborrhea of the scalp may also closely resemble psoriasis of the scalp and there is probably some relationship between psoriasis and seborrhea although the nature of this relationship is not known.

Seborrheic dermatitis is characterized by:

Scaling patches of varying size and shape. Scales may be dry or greasy.

Usually fairly well circumscribed except on the face.

There are two principal forms (3):

1. *A scaly, erythematous type* of eruption affecting the seborrheic areas—the scalp; the vertical third of the face; the eyebrows; the chest (presteral and interscapular areas), and the pubic regions.

2. *A moist, fissured type* attacking the flexures, especially the postauricular and inguinocrural regions; the intergluteal cleft; the umbilicus and the axillae. This type particularly must be differentiated by smear and culture from fungus infections.

As stated previously, seborrheic dermatitis in early infancy may pass by almost imperceptible stages more or less rapidly into typical atopic dermatitis. This occurs so commonly as to suggest a possible etiological relationship between the two diseases. The older the infant the less likely is this to occur. Also, atopic dermatitis and seborrheic dermatitis in infancy very commonly coexist. If there is any question about the diagnosis it is best to treat as though the condition were atopic dermatitis, because the local treatment for atopic dermatitis is commonly very effective for seborrheic dermatitis. Whether or not the early treatment of seborrheic dermatitis will prevent the subsequent development of atopic dermatitis has never been determined. It is, however, of some importance to make a differential diagnosis between the two diseases for these reasons:

1. If one is certain that the condition under study is seborrheic dermatitis there is no necessity for skin testing, elimination diets, etc., so the patient will be saved considerable trouble, time, and expense. It is necessary to treat only the local condition.

2. From the prognostic standpoint, about 80 per cent of patients with atopic dermatitis subsequently develop other allergic syndromes, whereas this occurs in only 25 per cent of the patients with seborrhea (2). This high percentage of infants with seborrhea who subsequently develop allergic disease indicates either that these infants have a greater tendency to develop such diseases than normal infants or, as is probably more likely, indirectly corroborates the experience that it is impossible, in some instances, in this age group, to make a differential diagnosis between seborrheic and atopic dermatitis.

DIFFERENTIAL DIAGNOSIS

The following signs and symptoms, which are not invariably present and which are also not pathognomonic, may occasionally be of help in differentiating between seborrheic and atopic dermatitis:

1. Seborrheic dermatitis of the general body surface is commonly accompanied by seborrhea of the scalp. However, what at times may appear to be a seborrhea of the scalp may be an atopic dermatitis. This is evidenced by the fact that the scalp lesions may clear at the same time as the general cutaneous manifestations following a general therapeutic measure as, for example, the substitution of soy

bean milk for cow's milk.

2. The color of seborrheic lesions contains more salmon, yellow or brown and less red than atopic dermatitis.

3. In the cubital and popliteal fossae the lesions of seborrheic dermatitis are more intense at the periphery and clearer in the skin over the creases. This is opposed to atopic dermatitis where the lesions are more marked, as a rule, over the joint creases and become less marked the farther the lesions extend from the joint creases.

4. The flexural lesions of atopic dermatitis tend to taper off very gradually from the creases of the flexures and, in the case of the cubital and popliteal fossae particularly, tend to extend continuously much further along the extremities than is the case with seborrheic dermatitis. Here the lesions tend to end rather abruptly where the skin surfaces are longer opposed when the joint is flexed, or the tissues come together in various body folds.

5. In seborrhea, particularly on the general body surface, the lesions may consist of waxy plaques. When the skin is tensed, a yellowish color appears. The waxiness of the seborrheic lesions is occasionally accompanied by more or less "brittleness" of the surface of the involved area. When this occurs about the mouth, for example, cracks will appear in the form of fine lines radiating out from the mouth transversely through the skin perpendicular to the direction of the fibers of the orbicularis oris. This somewhat thick, waxy lesion is seen more frequently elsewhere on the body and occurs particularly on the calves in early infancy. Here the fine, linear, radial markings do not appear because there are no muscles attached to the skin. This might well be termed seborrheic dermatitis "en cuirasse."

The scales of seborrheic dermatitis are of the "potato-chip" or "potato chip crumb" type, i.e., their edges tend to be somewhat curled. In atopic dermatitis the scales tend to be whiter, do not tend to be large and the edges do not curl as much.

6. There is much less itching with seborrheic than with atopic dermatitis and, hence, scratch marks and evidence of secondary infection are not so frequently found. The little indurated papules so characteristic of chronic secondary infection as a result of scratching in atopic dermatitis are conspicuous by their absence in seborrheic dermatitis.

7. There is no vesiculation in seborrheic dermatitis.

8. Lichenification does not occur in seborrheic dermatitis in infants and children.

9. Occasionally in seborrheic dermatitis there is observed a condition which might well be termed "tessellation." In this manifestation delicate, red vein-like lines are seen as if fine blood vessels were present and this may give to the skin in that area a tessellated or checker-board appearance. This is due to the acutely inflamed and red skin showing through very slender cracks in the overlying seborrheic crust. This does not occur in atopic dermatitis.



FIG. 18. (RGH 5597) Seborrheic dermatitis in a boy six and one-half months of age.

10. Occasionally the borders of the seborrheic areas are somewhat serpiginous in outline. This occurs much less frequently with atopic dermatitis.

11. Occasionally the skin may have a kind of oily or greasy "sheen" which does not occur in atopic dermatitis.

12. Depigmentation may occur in portions of the skin which have in the past been involved by chronic atopic dermatitis. This is particularly noticeable during the summer when adjacent areas of the skin may be well tanned. This depigmentation is not permanent.

and does not occur at all in children as a result of seborrheic dermatitis.

Figure 18 illustrates a very typical seborrheic dermatitis with large, fatty scales of the "potato-chip" type. Figure 19 illustrates typical seborrheic dermatitis with extensive involvement of the face. This shows the typical "potato-chip crumb" type of scale with upward-curling edges. When seen seventeen days later the character of the skin lesions had changed so that its appearance was typical of atopic dermatitis. There was also an accompanying increase in itching resulting in mild secondary infection.



FIG. 19. (RGH 9234) Seborrheic dermatitis. Boy six months of age.

One of the most common forms of intertriginous seborrheic dermatitis occurs in the postauricular folds and is quite common in early infancy although it may occur at any age. Figure 20 illustrates this in a sixteen-year-old girl. This case is particularly interesting because when she was seven years of age she was seen with what appeared to be a very severe seborrhea involving all of the scalp. Dr. Henry Shaw, who saw the patient in consultation, diagnosed psoriasis. Under his care this cleared in the course of time except for the intermittent occurrence of the lesions behind her ears and she was eventually referred back to me by another physician who had diagnosed "eczema." An instance like this is suggestive evidence, at least, that there is some link as yet to be discovered, between psori-

Courtesy Jerome Glaser, M.D., from the Department of Photography
of the Rochester General Hospital, Rochester, New York.



FIG. 20. (RGH) Postauricular seborrheic dermatitis in a 16 year old girl.

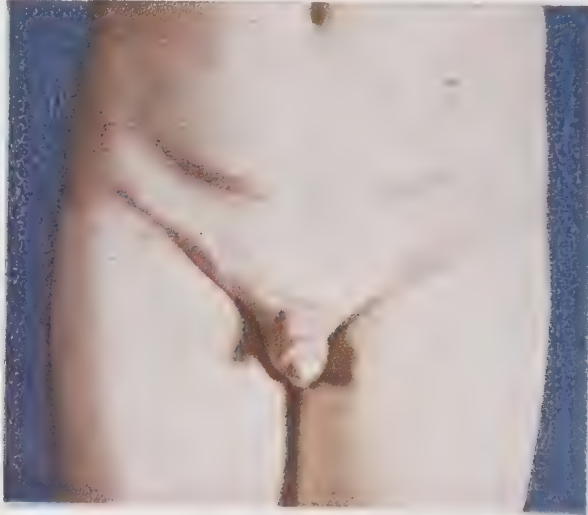


FIG. 21. (RGH 500) Boy ten years old. Intertriginous seborrheic dermatitis.

asis and seborrhea. When revealed, this should add considerably to our knowledge of these two baffling diseases.

Figure 21 illustrates a less common type of intertriginous seborrheic dermatitis. This was a stocky boy and whenever he sat down

the involved areas were covered by folds of flesh. For a considerable period the lesions were thought to be due to fungi but smears, cultures and skin tests were negative. Eventually the diagnosis of seborrheic dermatitis was made by Dr. Rudolf L. Baer. These lesions were highly resistant to treatment and still recurred occasionally particularly during the summer after swimming, until the boy was seventeen years of age.

Figures 22 and 23 illustrate some of the other diagnostic features



FIG. 22 and FIG. 23. (RGH 5434) Typical seborrheic dermatitis in a six month old girl.

of seborrheic dermatitis. Kodachromes do not always reproduce the faint shades of yellow and pink completely satisfactorily, yet these figures nicely illustrate the typical yellowish-brown or salmon colored lesions of the disease. The fairly sharply circumscribed patches are well illustrated in Figure 22. Figure 23 clearly shows, on the leg on the left hand of the observer, the central clearing of seborrheic dermatitis and the more strongly marked periphery of the lesion so typical of flexural seborrheic dermatitis, in marked contrast to atopic dermatitis which has just the opposite characteristics. The abrupt ending of the seborrheic lesions where the skin folds are no

longer in close opposition when the joint is flexed is also clearly illustrated.

It is interesting that in Letterer-Siwe's disease skin lesions identical with or very similar to those of seborrheic dermatitis may occur much more commonly than lesions resembling atopic dermatitis. A number of patients with Letterer-Siwe's disease have been seen who were mistakenly treated for seborrheic dermatitis. In one such instance, what should have been diagnosed as seborrheic dermatitis was mistakenly treated for atopic dermatitis with dietary measures so extreme that the infant developed scurvy. When seborrheic dermatitis in infancy is severe and generalized or intractable, Letterer-Siwe's disease should always be considered.

Preliminary studies have been made of dried smears of the exudate of the weeping areas in both atopic and seborrheic dermatitis with the thought that the cytology might be of assistance in making a differential diagnosis and even assist in making an estimation as to how much of the rash might be due to atopy and how much to seborrhea. Thus far the smears have shown only amorphous material, epithelial cells, and polymorphonuclear leucocytes, and the number of the latter appears to vary with the degree of local infection. Eosinophils are commonly conspicuous by their absence. However, the studies along these lines are being continued.

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TREATMENT OF SEBORRHEIC DERMATITIS

If the seborrhea is mild and limited to the scalp, often all that is necessary is to keep the scalp clean with soap (preferably a tar shampoo) and water. In slightly more stubborn cases a mild tar ointment (2 per cent crude coal tar in Lassar's paste) may be applied to the scalp at night and washed off with soap and water the next morn-

ing. The following ointment is very effective, particularly in early infancy and childhood:

Salicylic acid	1.8
Sulfur ppt.	2.0
Burroughs-Wellcome greasless ointment base	qs ad 60.00
Sig: Rub into the scalp 2 or 3 times a week at night and wash out the next day.	

Pragmatar (see Chapter 18) is also very useful on the scalp and often on the general body surface if the skin is chronically involved.

Vioform (Ciba) in 3 per cent ointment or cream (Chapter 18) is one of the most effective preparations available for seborrheic dermatitis (4, 6). It may occasionally be combined with crude coal tar:

Vioform (Ciba)	
Crude coal tar	aa 1.8
Lassar's paste	qs ad 60.00

In the treatment of seborrhea of the scalp sodium sulfacetamide has proven very effective and is now the method of choice in my practice in older children and adults although we have also used it very effectively in young infants on involved areas other than the scalp. Sensitization of the scalp or of the skin of the general body surface with resulting dermatitis has not been observed in my work although this has been reported in ophthalmological practice (5) and has occurred on the eyelids in one of my child patients.

Sodium sulfacetamide is a sulfon dug which is the mono-hydrated sodium salt of N-sulfanilylacetaimide. This drug appears to be generally useful against many Gram negative and Gram positive bacteria although I have used it only for seborrheic dermatitis which is not generally infected, and for marginal blepharitis believed to be of seborrheic origin.*

For treating seborrhea of the scalp, a 10 per cent cream-type lotion (water washable) is employed.† A sufficient amount of the lotion is rubbed in at bed time to moisten the scalp; the hair is brushed for two or three minutes and the medication allowed to remain in place overnight. This procedure is repeated for eight to ten

* For ophthalmic use the drug is supplied as 10 per cent sodium sulamyd ointment or eye drops (Schering).

† Supplied as Sebizon (Schering) in a 4 oz. plastic squeeze bottle.

nights. If the scalp and hair are oily or greasy, application should be preceded by a non-irritating shampoo. Weekly or biweekly applications may prevent recurrences. If there is severe primary or secondary bacterial infection, the lotion may be applied up to four times a day if necessary.

A selenium preparation (Selsun, Abbott) is also exceedingly helpful in the treatment of seborrhea of the scalp in older children and adults (1). This is applied as follows:

1. Wet head thoroughly with warm water, wash with soap and water or the usual shampoo, and rinse.
2. Shake bottle well. Pour an amount equal to one or two teaspoonsful into the palm of the hand and work into scalp with the addition of a small quantity of warm water until a lather is obtained.
3. Rinse and repeat process.
4. Allow preparation to remain in contact with the scalp for a total of at least five minutes.
5. Rinse scalp by using three or four changes of water or by showering thoroughly with running water.

Applications should be made twice a week until the condition is under good control and then continued as long as may be necessary, usually indefinitely, for once a week although occasionally longer intervals are satisfactory.

A selenium jelly is now available* which is said to be useful in the treatment of marginal blepharitis (2) although if used for this purpose care must be taken to avoid the conjunctiva where it is very irritating. The same preparation may also be used for treating seborrhea of the glabrous skin. For exudative lesions Rosen's 1-2-3 ointment (see Chapter 17) or 2 per cent aqueous gentian violet or both together has been found very satisfactory just as in the case of atopic dermatitis. Steroid preparations, systemically or locally, seem to be somewhat less satisfactory in the treatment of seborrheic dermatitis than in atopic dermatitis but may be used in the same way.

Many of the measures used in the local treatment of atopic dermatitis as discussed in Chapter 17 will also be found useful in seborrheic dermatitis.

* Supplied as Selsun sulfide (selenium sulfide, Abbott) 0.5 per cent jelly in 7.5 gm. (¼ oz.) tubes.

Vitamins, particularly those of the B complex, have long been used in an attempt to treat this disease systemically because of the similarity of skin diseases produced in animals on diets deficient in various portions of the B complex. However, as indicated in the review by Gans (3), there is no evidence that the disease in man is due to a vitamin deficiency or can be cured by administration of vitamins.

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CHAPTER 24

ERYTHRODERMIA DESQUAMATIVA

THIS DISEASE was first described by Carl Leiner (5), a Viennese pediatrician, in 1907. His original report was published somewhat later in English (6). As originally described, the disease affected mostly breast fed babies (probably because at that time most of the babies were breast fed). The essential characteristics of the disease are:

Onset at the age of four to twelve weeks, rarely later.

Generally starts on the scalp with the formation of thick, yellow fatty scales and crusts (*seborrheic dermatitis*). These are easily removed leaving an inflamed but not ulcerated skin. It is because of this that the disease is classified under *seborrheic dermatitis*.

The face is slightly inflamed and covered with thin, yellow scales. The trunk is red and at first covered with greyish-white opaque scales. These may become quite large and desquamate in a manner suggesting *potato chips*, leaving a slightly inflamed epidermis.

The hands and feet may become red, commonly only in circumscribed spots. Various deformities of the nails may occur. The disease is commonly accompanied by *gastrointestinal disturbances*.

The European mortality was high, about 1/3 of the cases terminating fatally.

In this country, erythrodermia desquamativa is very rare and apparently occurs in a much milder form than in Europe. Two cases seen by the author, however, at Strong Memorial Hospital, and the only cases seen there over a 25 year period, ran a very stormy course complicated by severe respiratory and gastrointestinal disturbances and would undoubtedly have died were it not for the use of sulfon drugs and antibiotics, plus the liberal use of transfusion.

Erythrodermia desquamativa may be confused with atopic erythroderma. However, a differential diagnosis should easily be made because of the following points which diametrically oppose the find-

ings in atopic erythroderma (4). In erythrodermia desquamativa there is:

Little itching.

No vesiculation.

No general lymphadenopathy.

No eosinophilia.

Skin tests negative.

Duration not over three months.

Recovery permanent.

No allergic sequellae.

Erythrodermia desquamativa must be further differentiated from dermatitis exfoliativa neonatorum (Ritter's disease). However, Ritter's disease characteristically begins with a circumoral erythema which becomes generalized and is not characteristically accompanied by seborrhea of the scalp. In Ritter's disease Nikolsky's sign (outer layer of skin easily rubbed off on slight pressure) is typically positive while in erythrodermia desquamativa this sign is negative. Psoriasis may occur in this age group but is distinguished by the fact that typical fine bleeding points occur on removal of the scales and the infants show no manifestations of systemic illness.

The first case in the United States was described by Greenthal (2) in Wisconsin, in 1930. Hill (3), in 1934, stated that in a series of approximately 800 cases of "infantile eczema" he had seen only twenty-one who fit into the erythrodermia desquamativa group. However, his description suggests that he included in this group patients which he later classified as atopic erythroderma. Thelander (8), in 1947, reported a typical case which was later reported (9) as having been followed by the celiac syndrome. Stadler and Byrne (7) described two cases but in one there was no gastrointestinal disturbance which possibly rules it out as a true Leiner's disease, although I believe I have seen the milder forms of this disease without gastrointestinal disturbance. The other case occurred in a Negro child and is the first to be reported in this race. The case reported by K. Glaser and Markson (1) was probably atopic erythroderma rather than Leiner's disease. The two cases at the Strong Memorial Hospital were diagnosed by the OPD residents on the basis of severe seborrhea complicated by severe gastrointestinal disturbance, as had been emphasized in my lectures on this subject to the house staff. One of these was a



FIG. 24. (SMH) Boy nine weeks of age—erythrodermia desquamativa showing marked seborrhea of face.

Negro child, the second to be reported in the colored race. This patient is illustrated in Figure 24. Both cases ran a very severe, stormy course but eventually recovered completely. The treatment is purely symptomatic.

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CONTACT DERMATITIS

Eczema venenatum; dermatitis venenata; epidermitis (Epstein (2)

THIS is the most common form of allergic dermatitis in adults but, in its milder forms particularly, is not uncommon in children. In a series of 516 allergic infants and children its incidence was 1.55% as compared with an incidence of 12.9% in a series of 200 adults (Table II). The figures for children, however, include only those cases in which consultation was sought for the dermatitis and exclude the milder forms of circumoral contact dermatitis and also the very common ammoniacal dermatitis, as this occurs so frequently as to be almost physiological.

According to Hill (4), contact dermatitis is characterized by: *Hypersensitivity of the epidermis to one or more substances of almost any composition. There is no hereditary factor. Reactions are erythematous, vesicular, bullous and of the delayed type (i.e., do not appear immediately as will scratch or intradermal tests but may require forty-eight to seventy-two hours or longer to develop). The bulla, although not always present, is the typical lesion of contact dermatitis and does not occur in any of the other forms of eczematoid dermatitis. Patch tests are typically positive. Scratch and intradermal tests are commonly negative. Passive transfer tests (patch) are almost always negative.*

The direct exciting causes of contact dermatitis may be divided into two groups:

(a) *Agents which do not affect the normal skin even after customary prolonged exposure, as soap, water, silk, wool, cosmetics, clothing dyes, etc.*

(b) *Agents which may affect the normal skin, even after slight exposure, the so-called PRIMARY IRRITANTS, usually chemicals, as acids, alkalis and salts.*

TECHNIC OF PATCH TESTING

The patch test has the same relationship to contact dermatitis that the scratch and intradermal tests have to atopic dermatitis, except.

possibly, that positive tests are more likely to be of clinical significance. Patch tests are very simply performed by applying some of the substance to be tested to a piece of blotting paper about 1.5 cm. square, applying this to the skin and covering with a piece of cellophane about 2.5 cm. square and, in turn, covering this with adhesive. If the skin is sensitive to adhesive, Scotch cellophane tape may be used. Lists of standard strengths for patch testing materials may be found in Urbach and Gottlieb (10). If there is any question concerning this, then tests must be made with the same substances on other individuals used as controls. It is essential that the concentration of the material used for patch testing should be such that it will not react on the normal skin in the manner of a primary irritant. The area of the skin to be patch tested should be as close to the affected area as practical. In many instances the skin of the V of the neck in front and in back will prove satisfactory. Bandages may be necessary, particularly in children, to hold the patches in place. The patches are commonly removed and the tests read at the end of forty-eight hours. They should be reread twenty-four hours later, after the local inflammation due to the mechanics of the patch testing has subsided. Occasionally very violent reactions, either local or general, are obtained and the patient should be cautioned to remove the patch should any untoward sensations be noted.

Dermatitis of the contact type on skin of the face about the mouth (circumoral contact type dermatitis) occurs quite frequently in infancy and early childhood from contact with foods as they are being fed, particularly spinach and carrots; less frequently from tomato and orange juice (see Fig. 9). Because the dermatitis occurs only on contact of the skin with these foods, they may be eaten without harm otherwise. This, also, is a type of dermatitis from which rapid spontaneous recovery is the rule. Next to contact dermatitis from urine, this is the most common type of contact dermatitis in this age group.

Contact type dermatitis from urine is the most common type of dermatitis in early infancy and childhood, and few infants escape this, at least in some degree. The dermatitis is commonly at first due to ammonia, liberated from the urine by the action of the micrococcus ureae from the stools on urea which first acts as a primary irritant. After more or less prolonged contact, the skin is sensitized

to ammonia so even minute amounts will react on the skin causing an allergic contact type dermatitis.*

Circumanal dermatitis may be caused by the mercury in the solution in which rectal thermometers are commonly kept in some hospitals. Another form of circumanal or perianal dermatitis of the newborn which has been studied by Pratt and Read, Jr. (6a) is frequently seen in early infancy. There is an irritation of the skin immediately about the anus, varying up to 4 cm. in diameter, erythematous and frequently exudative. Severe disease is characterized by multiple small, superficial ulcerations, while mild disease may be missed unless the buttocks are manually separated. This occurs in bottle fed babies (cow's milk) and is due to irritation of the skin by a rise in pH above the range found in breast fed infants. Perianal dermatitis is not to be confused with the diaper rash, which occurs later and affects the convex surfaces of the thighs and buttocks and is due for the most part to irritation by ammonia as described above.

Wool very often causes contact dermatitis by *mechanical irritation* by virtue of that very property, roughness of the fiber, which makes it so useful for weaving into cloth. As mentioned previously, wool is also an important cause of atopic dermatitis, by contact, and Peck and Salamon (6) found feathers of great importance in this respect. Soap is perhaps much more often a cause of contact dermatitis than is generally suspected, and the substitution of soap by other detergents may occasionally clear a stubborn case. Water itself, perhaps by reason of its hypotonicity, causes a contact dermatitis in some children as evidenced by the fact that improvement may occur when colloidal baths are substituted. In older children, during the winter a stubborn type of contact dermatitis, in which the factor of atopic dermatitis by contact may also be involved, commonly occurs. The usual areas of occurrence are those of direct contact by snow suits around the wrists, ankles and neck due to the interaction of various factors, as wool, dye, moisture from the melted snow, cold and body heat.

Figure 25 illustrates a very severe contact type dermatitis from a quinine compound formerly used as an antiseptic in a very popular brand of baby oil. Because of reactions like this, a less harmful antiseptic was substituted. The blue discoloration of the infant's skin

* Samuel W. Clausen, Unpublished work.



FIG. 25. Contact dermatitis in a boy one month of age following application of a baby oil.



FIG. 26. Contact dermatitis in a boy 5 years of age from a toilet seat.

was due to the application of gentian violet for the treatment of a secondary infection. Following discontinuance of the oil applications, the infant made an uneventful recovery.

Occasionally the pattern produced by the irritant causing the contact dermatitis will give a very definite clue to the source of the irritant. Such an instance is illustrated in Figure 26. The boy was five years old when first seen and had been under the care of the

leading pediatrician in a large eastern city. When he was about two years of age, a dermatitis appeared on his buttocks which was diagnosed as "eczema." Local treatment proved unavailing, but whenever the child was taken to the seashore, where the family spent the summer, the skin healed nicely, thus attesting to the marvelous virtues of sea air and confirming the observation that eczema is usually less troublesome in the summer than in the winter. The mother was told that the child would outgrow the eczema and that it was unnecessary for him to be studied by an allergist. In this family, there were two physicians (neither of whom was a pediatrician, dermatologist or allergist). They told the mother that she should stay away from the allergist since he would only subject the child to innumerable tests, next to impossible diets, and other useless procedures, all of which would be of considerable expense to the family without yielding any solution to the problem. However, the condition became so intolerable that the mother finally brought the child into the office. The diagnosis of dermatitis due to contact with the toilet seat was made on a moment's inspection without the necessity of doing cutaneous tests and the other procedures the mother had been warned against. As soon as she heard the words, "toilet seat dermatitis," she exclaimed, "Why, I should have thought of that myself. Every time I put him on the toilet, he rubs himself around against the seat and scratches himself."

TREATMENT OF CONTACT DERMATITIS

Contact dermatitis cannot be satisfactorily treated unless the cause is found and removed. Symptomatic medication may be employed to relieve itching and protect and sooth the affected parts. Antihistaminics orally and locally are sometimes of help. The work of Cole (1) suggests that dimercaprol (BAL) ointment will prove of value when the dermatitis is due to local preparations containing heavy metal salts (as mercury ointments) and to metals directly. For prophylaxis against contact dermatitis, silicone, and other types of protective ointments are now coming into general use. Great care must be exercised not to irritate the skin by overtreatment or to sensitize it to the medications used.

One of the best treatments for the acutely inflamed stage is the application of Burow's solution soaks followed by the 1-2-3 oint-

ment of Rosen. These preparations and their method of use have been discussed in Chapter 17. Hydrocortisone acetate ointment and lotions in concentrations of 1% and 2.5% have also proven extremely useful although the role of this drug in the local treatment of contact dermatitis has not yet been fully evaluated.

POISON IVY (RHUS TOXICODENDRON) DERMATITIS

While important at all ages, this disease presents a special problem in children because of their constant outdoor playing. Poison ivy and the related plants, poison oak and poison sumac, all contain polyhydric phenols which differ only slightly in their chemical formulae and which are the dermatitis producing constituents of the plants. The toxins are for all practical purposes immunologically identical and susceptibility to one renders the patient susceptible to all. Japanese lacquer also contains a chemically similar principle which will cause a similar type of contact dermatitis in individuals sensitive to these plants. The dermatitis caused by the plants has no distinguishing characteristics which will permit an exact etiological diagnosis. The appearance is exactly the same as that produced by any other of the less common forms of contact dermatitis caused by other plants such as primrose, chrysanthemum and ragweed. The specific etiological diagnosis can often be made from the history or from patch tests which must be most carefully done to avoid causing a severe dermatitis.

I have never used the injection method for the prophylaxis of rhus dermatitis in children. The method of oral hyposensitization described by Schamberg (8) has proven highly satisfactory. The prescription given the patient is as follows:

Tincture of rhus toxicodendron	1.0
Ethyl alcohol	5.0
Syrup of orange, qs ad	120.0

The patient is instructed to take the mixture in half a glass of water after meals as follows:

<i>Breakfast (Drops)</i>	<i>Lunch (Drops)</i>	<i>Dinner (Drops)</i>
1	2	3
4	5	6
7	8	9
10	11	12
13	14	15
16	17	18
19	20	21

When the dose of twenty-one drops has been reached, for purposes of convenience and simplicity, the child may now be given a teaspoonful in half a glass of water *once a day only*. This should be continued throughout the ivy season. If a patient experiences any disagreeable reaction to the treatment, the first evidence of which is more or less generalized pruritis, the dosage should be reduced a few drops below that point and no attempt made to increase and continued as the maximum dose through the remainder of the ivy season. According to Schamberg, the immunity (if one may call it that) established after a month's administration will persist for about a month afterwards. After this, susceptibility is prone to return. Schamberg states that the same mixture appears to exert a favorable influence on ivy poisoning in preventing an extension of the process, and in shortening the duration of the attack. The procedure, with which I have no personal experience, is administered as follows:

<i>Breakfast (Drops)</i>	<i>Lunch (Drops)</i>	<i>Dinner (Drops)</i>
2	4	6
8	10	12
14	16	18

This is then followed by a teaspoon once a day, well diluted.

Shelmire (9) uses a highly refined oleoresin of poison ivy administered in capsules for prophylaxis.* Goldmann (3) has found this highly satisfactory in the treatment of children who are able to swallow capsules.

The oral administration of the rhus toxin is not without danger. As indicated above, pruritis may be the first indication of overdosage. Other much more serious complications may occur. Lowenberg (5) reported an eleven year old boy who, following the administration of tincture of rhus toxicodendron, developed headache, high fever, nausea, vomiting, pulmonary signs suggestive of pneumonitis, and severe convulsions. Complete recovery occurred in about two weeks.

My experience in the treatment of the acute attack by the injection method corroborates the observations of Reyer (7) who feels that injections of antigen do more harm than good.

Efforts, however, to find a suitable material for injection purposes continue. One of the most promising appears to be the preparation

* This material may be obtained from the Graham Laboratories, Willow Lane, Route 7, Dallas, Texas.

of Strauss and Spain (9a) which is an aqueous alum precipitated pyridine extract.* This has been very favorably reported upon by Gaillard (2a). The most satisfactory drugs at present for the treatment of this disease are ACTH and cortisone which are ideal for the short term therapy which is commonly all that is necessary. The same doses may be used as in the treatment of atopic dermatitis (Chapter 19). For local treatment one may use a bland shake lotion, as calamine with one per cent phenol or the following shake mixture:

Phenol	1.0
Zinc oxide	
Talc aa	20.0
Glycerin	
Water aa qs ad	120.0

The antihistaminics are worth a trial, orally and locally, but are not usually very helpful, and sedatives may be used as necessary.

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* Obtainable from String, Cobb & Co., Cleveland 4, Ohio.

ECZEMATOID DERMATOSES OF BACTERIAL ORIGIN

IT SEEMS reasonable to suppose that atopic dermatitis due to sensitization to the bacterial flora of the skin, or to bacteria involved in acute or focal infections, might occur. Pillsbury (7) has advocated a trial of penicillin in clearing up long standing cases of eczema. In a few instances, in young children, I have been unsuccessful in attempting to relieve intractable atopic dermatitis by the use of autogenous vaccine made from the skin flora or by the use of penicillin. It is of some interest in this connection that Rostenberg *et al.* (8) found that the bacterial flora of the skin of atopic and non-atopic individuals does not differ. MacDonald (4) has reported focal infection in adults as causing atopic dermatitis. Chobot (1) reported a seventeen month old boy who responded to vaccine made from infected tonsils.

While there appears to be but little doubt that focal infection may be related to atopic dermatitis, the exact nature of this relationship remains to be determined. Norrlind (5), in an investigation of one hundred adult patients with atopic dermatitis, found that of thirty-nine who had histories of exacerbations of the dermatitis in connection with acute respiratory infections, thirty-seven showed positive reactions to bacterial allergens. In two instances there was a flare-up of the eruption following skin testing, and in two others almost complete recovery followed removal of foci of infection. On the contrary, of fifty-eight patients who had never noted aggravation of the dermatitis in association with respiratory infections, positive skin reactions were found to bacterial allergens in only seven. He concluded that in some adult patients with atopic dermatitis, acute respiratory infections or focal infections may aggravate the cutaneous disease and that skin tests with bacterial allergens are useful aids in establishing the importance of such infections in individual cases. Sulzberger and Baer (9) apparently accepted Norrlind's observations, stating that

they had seen numerous flare-ups of atopic dermatitis in infants and young children after receiving prophylactic vaccinations for smallpox, pertussis, diphtheria and influenza. However, they (10) felt that it was not necessarily an immunologic reaction based on specific hypersensitivity to bacterial or viral allergens which produced the exacerbations. My experience over many years with infants and children is not in accord with the observations of Sulzberger and Baer although so far as influenza vaccine is concerned, I have not used it in these patients because so many are egg sensitive. In my experience, also, acute respiratory infections, as well as febrile infections of any type, are followed by at least temporary clearing of atopic dermatitis in most cases. Rostenberg *et al.* (8), in a study having the same objectives as that of Norrlind could demonstrate no evidence of the bacteriologic etiology of atopic dermatitis.

INFECTIOUS ECZEMATOID DERMATITIS

Occasionally a chronic, purulent discharge may cause an eczematoid reaction by contact with the previously normal skin of the adjacent area. In children this most frequently happens due to a chronically discharging ear, a very rare occurrence since the advent of modern anti-infectious therapeutic methods. This may sometimes be avoided by protecting the skin surrounding the discharge area by a bland ointment. The new protective silicone ointments are very useful for this purpose.

Epstein (2) states that bacteria rank first in the causation of bacterial eczema, fungi next, and other parasites, such as mites, run a poor third. In general, bacterial or "infectious" eczemas are due to a combination of an infection and an eczema. This association, according to Epstein, may occur in three different ways:

1. Infection of the skin may lead to an eczematous sensitization to the causative organism. This corresponds to the classical concept of infectious eczematoid dermatitis.
2. An infectious process of the skin may become complicated by a dermatitis of a different nature, for instance, a contact dermatitis.
3. An eczematous dermatitis may become complicated by secondary infection.

Infectious eczemas may be complicated by various forms of sensitization, such as bacterial contact or autosensitization. This may

lead to an "id"-like generalized eruption. The causative bacteria in infectious eczemas are mainly staphylococcus aureus and streptococcus hemolyticus, although a variety of others may also be found. There is no one characteristic clinical picture, but sharp, polycyclic outlines or undermining borders are suggestive. Fortunately, in infants and children, such cases are not very common and the infections are commonly cleared without too much difficulty with the many potent antibacterial agents now available. For further details, Epstein's original work should be consulted.

Fungus eruptions (dermatophytoses and dermatophytids) are not



FIG. 27. Boy 16 months of age. *Monilia* infection limited to the feet.

particularly common in early childhood. The fungus infections most commonly occurring are the easily recognized lesions between the toes. In this age group the infection is most commonly due to *Monilia albicans* (see Fig. 27), whereas in older individuals the members of the *Trichophyton* group are more commonly found.

Hill (3) has called attention to the possibility that some of the eczematoid dermatoses of infancy and childhood of obscure origin may possibly be due to fungi, but this could not be positively proven even in the cases which he presented. The fact that this field of investigation has proven sterile as far as the allergic dermatoses of infancy and childhood are concerned is evidenced by the failure

of any significant reports on the subject to appear since Hill's publication in 1934, except for the negative report of Perlman *et al.* (6).

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NUMMULAR ECZEMA—CIRCUMSCRIBED NEURODERMATITIS

NUMMULAR ECZEMA

THIS CONDITION, which is illustrated in Figure 28, is characterized by the appearance of coin-like (hence the term “nummular”), round or oval lesions, and is uncommon in infancy and childhood. It has been excellently described by Hill (3) as follows: “Num-



FIG. 28. Nummular eczema. Boy 15 years of age.

mular eczema is characterized by sharply defined circular or oval patches, usually of a rather dark color, varying from the size of a dime to that of a silver dollar, occurring often on the extensor surfaces of the arms or legs. It may occur on any part of the body, including the face. The small patches are usually more nearly round than the larger ones which are sometimes irregular or oval in shape.

The individual patch is composed of innumerable very fine vesicles; the older and larger patches are always thick and boggy, always a little moist, but not 'weeping.' The patches occasionally clear a little in the center, but not as much as patches of ringworm do, nor do they, on close examination, resemble patches of seborrheic dermatitis. They are thicker and more moist and usually of a darker color. The patches of nummular eczema are more regular in outline than those of atopic dermatitis; there is a sharper line of demarcation between the diseased and healthy skin; the larger ones are more "boggy" and exudative, and there is no lichenification. Itching may be almost absent or moderate; there is never the severe itching such as in atopic dermatitis. The skin, except for the circumscribed patches, is smooth and of good quality. The scalp is not involved."

Nummular eczema is chronic and recurrent and the lesions are "fixed," i.e., they recur in the same sites. Although many individuals with nummular eczema give positive skin tests to foods and other allergens, management from the allergic standpoint, in my experience, has been completely unsatisfactory except for one case in an infant whose rash was easily shown by means of elimination diets to be due to specific foods. Cope (2), in some instances in adults, has found food allergy potentiated by focal infection as an etiological factor.

Perlman *et al.*, (5) have discussed this condition in considerable detail. They reported six cases occurring in five children, the oldest four years of age, and one infant a year of age. Five of these six patients had a definite history of allergy. The histological picture is said to be variable, depending upon the duration of the lesions. In two cases reported by Sachs *et al.*, (6) it was that of a psoriasiform neurodermatitis, a condition generally recalcitrant to topical therapy with recurrence as the rule.

Sulzberger and Wolf (7) state that the lesions are best managed by mild antiparasitic treatment rather than with purely soothing antieczematous measures. Curiously, in this disease, roentgen therapy is only of limited value.

For the local treatment, Perlman *et al.*, favor 1 per cent ichthammol in a base consisting of equal parts of zinc oxide ointment and cold cream. They also use 1 per cent oil of cade in Rosen's ointment (see Chapter 17), and in one case used 1 per cent ichthammol and

1 per cent salicylic acid in Aquaphor (Duke), followed later by Superath (Talby-Nason). In three adults with nummular eczema, Sulzberger and associates (8) obtained no relief using a 1 per cent hydrocortisone acetate ointment. However, further studies with this preparation in stronger concentration are very much in order.

CIRCUMSCRIBED NEURODERMATITIS

Circumscribed neurodermatitis (lichen chronicus simplex circumscripta of Vidal) does not occur in infants (3) and not usually in early or late childhood, but is not uncommon in adults. When it does occur in childhood, it is usually the end-result of chronic atopic dermatitis and, therefore, occurs particularly in the cubital and popliteal fossae. It may be produced by long continued, localized scratching from any cause. There are not usually more than one to three patches and these may vary in size from 1.5 to 10 cm. They occur chiefly on the back or sides of the neck, especially of adolescent girls, and are occasionally seen on the extensor surfaces of the knees and elbows, the inner surfaces of the thighs, about the ankles and occasionally in other locations.

The lesions are sharply circumscribed and usually slightly raised above the general skin surface. The color is generally, though not invariably, somewhat violaceous; the surface is dry and may be smooth, but in children is generally roughened with marked lichenification (exaggeration of the normal skin markings) with occasionally dry, greyish-white scales. Since these lesions itch, there may be scratch marks and excoriations and sometimes evidence of secondary infection.

On the extensor surfaces of the elbows and knees the disease must be differentiated chiefly from psoriasis (4), but the latter disease is usually recognized by the fact that there is usually less itching; the scales are silver white and may leave fine bleeding points when separated from their attachment (Auspitz phenomenon). Psoriasis is often accompanied by stippled nails and there are usually other psoriatic lesions elsewhere on the body.

Figure 29 illustrates circumscribed neurodermatitis in a boy two and one-half years of age, which is very young for this disorder. He had suffered from urticaria of undetermined origin for several months previously. It is believed that this patch of derma-



FIG. 29. Circumscribed neurodermatitis in a two and one-half year old boy.

titis was secondary to scratching from itching induced by the urticaria. The diagnosis of circumscribed neurodermatitis was confirmed by Dr. Clarence H. Peachey who felt that parapsoriasis could be ruled out. Figure 30 illustrates circumscribed neurodermatitis



FIG. 30. Circumscribed neurodermatitis in a 12 year old boy.

which occurred as the end-result in the skin of chronic atopic dermatitis in a twelve year old boy. The lesions were located in the cubital fossae. This beautifully illustrates lichenification which, as previously stated, does not occur in seborrheic dermatitis in infancy and childhood.

Circumscribed neurodermatitis does not respond to allergic management. Occasionally the lesions disappear spontaneously. Local measures employed in the treatment of eczematoid dermatoses may or may not help. Becker and Obermayer (1) recommend the following ointment to be applied twice a day:

Pine tar	
Salicylic acid aa	0.3
Zinc oxide	10.0
Lanolin qs ad	60.0

If this does not help, the tar and salicylic acid may be increased up to 5% each in children. Hydrocortisone acetate ointment in the few cases thus far studied has proven to be of great value, at least for temporary relief. Roentgen therapy does also although recurrences are common.

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BRONCHIAL ASTHMA IN INFANTS AND CHILDREN

A CORRECT diagnosis of bronchial asthma is ordinarily made without difficulty at any age. An incorrect diagnosis is perhaps more common in infants and children than in older individuals (6). There are two principal reasons for this: (1) congenital stridors of various origins are not rare at this age and often produce a wheezing type of respiration suggestive of bronchial asthma, and (2) unsuspected foreign bodies in the air and food passages occur more commonly in infancy and childhood than in older age groups and may cause symptoms simulating bronchial asthma to an exceedingly misleading degree. Little harm can be done by continued observation in most cases of congenital stridor but procrastination in the case of a foreign body may lead to very serious complications and even death. In all cases of wheezing of doubtful origin, a roentgenogram of the chest should be made and then, if there is any doubt concerning the presence of a foreign body, bronchoscopy is mandatory. Lell (10), in an exceedingly valuable bronchoscopic study of 176 children thought to be suffering from epinephrine-fast bronchial asthma, found that 130 had true bronchial asthma; thirteen had unsuspected foreign bodies in the bronchi; in fourteen there was tracheal compression from external causes; eight had organic changes in the larynx; five had foreign bodies in the esophagus; five others had foreign bodies in the larynx; and one had a retropharyngeal abscess.

It must never be forgotten that the diagnosis of bronchial asthma is a *clinical* and not a laboratory diagnosis. The patient should never be referred to the allergist for skin testing "to see if he has bronchial asthma." While in most instances a correct diagnosis can be made from the history alone and without examination of the patient, nevertheless the physician cannot positively state that a patient actually has bronchial asthma unless an examination has been made during an attack.

A suggested definition (6) of bronchial asthma, which, if adhered to closely should lead to a correct diagnosis is as follows: Bronchial asthma may be defined as a form of obstructive emphysema involving both lungs throughout, characterized by paroxysmal attacks of dyspnea, accompanied by wheezing, chiefly expiratory, heard on auscultation of the chest and typically relieved, at least in the early stages of an attack by sympathomimetic drugs. A continuous asthmatic state may supervene later but in the beginning, at least, there is always an interval of freedom between attacks.

To this might be added the fact that the attacks are chiefly nocturnal. However, the younger the child the less prominent is this particular feature. This definition emphasizes the important fact that bronchial asthma is only one form of obstructive emphysema. It is, however, the most common form. If this is kept in mind the use of the confusing terms, "non-allergic asthma" and "para-asthma" (12) may be avoided. All so-called asthmas in these groups are other forms of obstructive emphysema and should be so designated. The above definition, which is a definition of allergic bronchial asthma, depends for its accuracy upon the proof that the wheezing is caused by an antigen-antibody reaction. However, in the most troublesome form of asthma, the so-called "intrinsic asthma," these allergens cannot commonly be demonstrated. This fact, however, does not detract from the practical value of this definition. Dyspnea and wheezing alone are not sufficient to make a diagnosis because these accompany a multitude of conditions besides bronchial asthma as will be demonstrated subsequently.

Every part of the above definition must find an application if the attack is to be considered as true or allergic bronchial asthma. For example, bronchial asthma never involves part of the lungs. Both lungs are involved throughout except when certain complications, to be discussed later, occur. Similarly, the attacks of bronchial asthma are, at least at the beginning, always paroxysmal in character. Bronchial asthma never starts with an attack which persists indefinitely.

Expiratory wheezing as a diagnostic feature has been questioned. Kahn (8) stated "the prolonged expiratory effort, typical of the adult asthmatic . . . is frequently not seen in young children, especially infants, being replaced by what is apparently an ordinary dyspnea."

Buffum (2) stated that the wheezing, prolonged expiration and musical rales which are typical of asthma in later life, are often absent in infancy. Instead there is a noisy breathing with only moderate dyspnea, and on auscultation only loud tracheal rales are heard. This noisy breathing, which does not seem to be typical of anything, may lead one away from the diagnosis of asthma, which ultimately is made by other means. It is, indeed, very difficult in my experience to time the respirations accurately in the dyspneic infant, and the picture is further confused by the fact that the chest is small and round, and sounds are easily transmitted from different parts. Nevertheless, I have the impression that even at this age expiratory dyspnea is more marked than inspiratory and if this is not true then the diagnosis must be more carefully questioned than otherwise.

The wheezing of bronchial asthma must be heard on auscultation at the chest wall. In some forms of obstructive emphysema wheezing is not audible here although it can be demonstrated on auscultation of the patient at the nares or mouth. The following illustrates such a situation:

CASE NO. 4351. This was a boy, five and one-half months of age, who was referred for consultation because of bronchial asthma. The maternal grandmother had asthma and a brother eczema. The patient himself developed a rash whenever orange juice was ingested. He also had a seborrheic dermatitis involving the posterior auricular folds, the external auditory canals and the scalp.

The patient's illness was said to have started with a very severe cold early in June, and a bad attack of "asthma" occurred late that month. He seemed to suffer more outside of the house than inside. The symptoms cleared considerably when he was taken to a pollen-free resort. However, as soon as he returned to Rochester, which was in early September at the height of the ragweed pollen season, the "asthmatic attacks" recurred almost daily. Ephedrine gave no relief. The attacks had not been considered severe enough to require the injection of epinephrine. The history was consistent with bronchial asthma due to the pollen of grasses and weeds.

Upon physical examination, the boy was well developed and nourished, and lay comfortably on his back wheezing loudly. On closer observation it was evident that he had a definite inspiratory stridor with slight retractions of the costal margins. On auscultation



FIG. 31. Boy five and one-half months of age. Obstructive emphysema of unknown origin causing symptoms resembling bronchial asthma. (Left, inspiration; right, expiration.)

of the chest wall no wheezing could be heard. On fluoroscopy the lungs presented a remarkable picture which was confirmed by a roentgenogram (Fig. 31). The heart and trachea and other mediastinal contents were shifted over to the left side. There was a marked emphysema involving the major portion of the right lung with increased transparency. The diaphragm on the right side was depressed and partially fixed with increased excursions of the diaphragm on the left. These signs were most accentuated at the end of expiration and are typical of unilateral obstructive emphysema as described by Manges (11).

It was suspected that the etiological factor was a non-opaque foreign body in the right bronchus. The parents refused bronchoscopy. The mother was known to have active tuberculosis but a tuberculin test on the child was negative. He was seen seven months later at the age of one year and appeared to have developed normally with the chest findings remaining the same. He was not seen again until he was two and one-half years of age and at that time the chest by roentgenogram was entirely normal and he was symptom free. The cause of the obstructive emphysema in this instance remains unknown.

LATENT WHEEZING

If a child is seen between attacks and no wheezing is apparent on ordinary breathing, latent wheezing may often be demonstrated by inducing forced expiration. This method was first described by Clarke (4). If the child is old enough, usually over three years, cooperation may be obtained by asking him to "Blow hard, just like you blow out the candles on a birthday cake," or some similar request. I have observed that latent wheezing may be much better brought out if the patient, instead of blowing in the ordinary manner, will forcibly expire with the mouth widely open. In this way no back pressure is created by the act of blowing in the usual manner with the lips only partially opened and the wheezing rales are much more easily elicited. If the child is too young to cooperate, latent wheezing may sometimes be demonstrated in the manner described by Fineman (5). In this maneuver the thorax is compressed forcibly with the palm of the hand or forearm while listening with the stethoscope held against the chest wall by the other hand. I have found Fineman's procedure very useful at times.

If latent wheezing cannot be demonstrated by the above methods

the same effect sometimes may be produced by causing the child to become breathless from exercise, or in the case of an infant, by making him cry. This should bring out latent wheezing or, if wheezing is present, cause it to become exaggerated. The value of this procedure is illustrated in a negative sense in the following report:

CASE No. 6109. This boy was first seen at the age of seven months because of wheezing which had been observed since he was a month old. Because this was not at all troublesome he was not brought to a pediatrician until he was three months old, when the mother wished advice regarding feeding. At this time asthma was suspected and the diagnosis appeared to be confirmed when the wheezing stopped after the administration of a test dose of epinephrine. When seen for consultation four months later the child was still wheezing but the attacks continued to be very mild. There was no history of asthma in the immediate family although there was bronchial asthma on the maternal side. Physical examination was normal except for faint, high-pitched wheezing sounds on inspiration throughout both lungs. Fluoroscopy and roentgenograms in various positions revealed normal findings. On taking a post-nasal smear for eosinophils, the child cried vigorously, the wheezing disappeared, and no rales could be heard on auscultation of the chest. The mother then stated in response to questioning that the child had cried when given the test dose of epinephrine some months previously. I felt that the facts that the dyspnea was inspiratory and disappeared on crying ruled out bronchial asthma and that the child had a congenital stridor of undetermined origin.

FEVER IN CHILDHOOD ASTHMA

The problem of fever in relationship to attacks of asthma in infancy and early childhood has not as yet been studied in detail. In my own experience, uncomplicated bronchial asthma in this age group may be accompanied by a very slight increase in body temperature (over 37° C or 100° F rectally). This rise does not commonly amount to more than 1.5° F (0.8° C). It is probably due to the increased metabolism of muscular effort accompanying the dyspnea.

EARLY APPEARANCE OF EMPHYSEMA IN INFANTILE ASTHMA

One of the most interesting physical signs of bronchial asthma, or any other form of generalized obstructive emphysema in child-

hood, is the early disappearance of the normal area of cardiac dullness. This sign must be elicited with care as the area is normally very small at this age. A corollary to this is the increase in size of the clear areas in front of and behind the heart shown by fluoroscopy and roentgenograms in the lateral and oblique positions.

SYMPTOMATOLOGICAL DIFFERENCES BETWEEN INFANTILE AND ADULT ASTHMA

There are certain important differences in the symptomatology of bronchial asthma between children and adults. This is particularly true of children two years of age or less. This is probably correlated with the fact (9) that the infantile type of respiration, chiefly abdominal, changes toward the adult type, chiefly thoracic, beginning with the assumption of the upright position. This, as a rule, is well under way by the end of the second year.

It is often striking that the asthmatic infant may be perfectly comfortable, even when flat on his back (3). This is in significant contrast to the older child or adult where the absence of orthopnea may cause doubt as to the diagnosis. This is doubtless due to the type of breathing normal at this age and the greater softness and flexibility of the thoracic cage.

The absence of anxiety on the part of the infantile patient in a severe attack of asthma is in striking contrast to that of the adult. An infant may be wheezing loudly and apparently have great difficulty in breathing and yet his attention may be distracted and he may even be made to smile by dangling a rattle or other toy in front of his eyes. The parents are commonly much more anxious than the child. The only infants or young children I have seen who appeared very anxious were those who were unable to respond to the injection of epinephrine.

OTHER DIAGNOSTIC AIDS

RESPONSE OF THE ASTHMATIC ATTACK TO MEDICATION

It is important to remember that at one stage of its development bronchial asthma is always satisfactorily and completely relieved by the administration of a sympathomimetic drug (ephedrine, epinephrine, etc.). The relief, to be diagnostic, must be complete and un-

equivocal. The statement so often made in the physician's or nurse's notes to the effect that such a drug was given during an attack and "the patient appeared to be slightly improved," means nothing as regards the diagnosis. So far as I know, Ratner (13) was the first to emphasize relief by an appropriate drug as part of the definition of bronchial asthma.

The same kind of relief from intravenous aminophylline, where a possible cardiac factor as the cause of the dyspnea need not be considered, is probably also specific for the diagnosis of bronchial asthma. However, this cannot be stated with certainty until more information is available regarding the effect of aminophylline in forms of obstructive emphysema other than bronchial asthma.

NASAL EOSINOPHILIA

The demonstration of eosinophils in the mucous secretion of the respiratory tract is an important diagnostic procedure because if these are found in sufficient numbers, the burden of proof rests with the physician who states that the child does not have allergic disease.

My experience with direct smears of mucus from the nose or pharynx of young children was not uniformly successful, especially when the secretion was scanty, until it was discovered that continuous direct contact of the swab with the mucous membrane for at least one minute would almost always result in positive smears in the case of an allergic membrane. Infants and young children will not tolerate, even for a minute, the presence of tightly wound cotton, even when not attached to a wire or toothpick in their nasal passages without crying. The tears passing through the nasolacrimal duct into the nasal cavity wash the swab free of cells. However, on adapting the Bradford (1) post-nasal flexible wire swab for this test, it is relatively simple to obtain good smears. These swabs, which consist merely of a cotton tip thinly, tightly, and evenly wound around a thin strand of flexible copper wire, were originally devised by Bradford for taking post-nasal cultures for detecting the presence of pertussis bacilli. When adapted for the purpose of demonstrating eosinophils, the child is held firmly on his back, the swab inserted through a nostril until its tip rests against the vault of the pharynx, for a minute so that the tears will not flow back against the swab. The swab is then removed and a smear made which is then stained

by Hansel's method (7). A less satisfactory procedure, but also effective, is to close the openings of the nasolacrimal ducts with the fingertips while the child is forcibly restrained on his back and the nasal swab inserted.

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THE DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA

THERE are a number of excellent presentations of the problem of the differential diagnosis of bronchial asthma in adults, among the more practical of which may be mentioned, is that of Sodeman (6). Abramson (1) also has a very excellent discussion of this not only as regards adults but also children.

Table X represents an attempt to systematize most of the conditions in pediatric practice which may simulate bronchial asthma. The more important conditions mentioned in this table will be discussed in detail in the following pages.

Since noisy breathing is a cardinal sign of bronchial asthma, even slight variations in normal breathing may be interpreted by anxious parents as the first evidence of bronchial asthma, particularly in families who, because of the presence of the disease in a parent or sibling are worried about the possibility of asthma in their child. Even the stridor produced by the vibration of excess mucus in the nose or throat of the infant or by enlarged adenoids, or, more rarely, by a retropharyngeal abscess may be thought to be bronchial asthma. A correct diagnosis, reassurance of the parents and treatment of the underlying condition as indicated, is usually all that is necessary under such circumstances.

CONGENITAL LARYNGEAL STRIDOR

A fairly large proportion of infants under one year of age, and particularly infants in the first few months of life, referred for study because of bronchial asthma, do not have this disease but suffer from one of various forms of laryngeal stridor. The great majority of these stridors are inspiratory because the infantile larynx is soft and narrows on inspiration and expands on expiration. The mechanism of this has been reviewed by Crooks (3) who stated as follows: "The larynx has a folded epiglottis so that its posterior edges with

TABLE X

SOME OF THE CONDITIONS TO BE CONSIDERED IN THE DIFFERENTIAL DIAGNOSIS OF
BRONCHIAL ASTHMA IN INFANCY AND CHILDHOOD

- I. *Upper Respiratory Tract*—The nasal passages and pharynx.
 - (a) Mucous vibrating in the nasal passages.
 - (b) Foreign body.
 - (c) Tumors—Hypertrophied adenoids; neoplasms.
 - (d) Inflammatory reactions—retropharyngeal abscess.
 - (e) Inflammation resulting from odors, gases and dusts.
- II. *Middle Respiratory Tract*—Larynx, trachea and main bronchi.
 - (a) Foreign body in air passages or in esophagus.
 - (b) *Congenital anomalies*
 - Long, flaccid epiglottis
 - Relaxed larynx
 - Cysts
 - Anomalous folds of mucous membranes
 - Anomalous vessels, as double aortic arch
 - (c) *Mediastinal tumors or neoplasms*
 - Hodgkin's disease
 - Tuberculous adenitis
 - Enlarged thymus
 - (d) *Inflammatory reactions*
 - Croup
 - Laryngotracheobronchitis
 - Inflammation resulting from irritating odors, gases or dusts
 - (e) Recurrent laryngeal nerve paralysis
 - (f) Bronchotetany
- III. *Lower Respiratory Tract*—Lesser bronchi and subdivisions
 - (a) Foreign body
 - (b) *Inflammatory reactions*
 - Asthmatic bronchitis
 - Capillary bronchitis (bronchiolitis)
 - Atypical pneumonitis
 - Bronchiectasis
 - Bronchostenosis
 - Pulmonary changes of mucoviscidosis
 - Inflammation resulting from irritating odors, gases or dusts.
 - (c) Neoplasms
 - (d) Localized hypertrophic emphysema
 - (e) Ayerza's disease
- IV. *Other conditions*
 - Cardiac asthma
 - Sighing dyspnea
 - Post-encephalitic hyperpnea
 - Stridor due to cerebral palsy

anterior attachments of the ary-epiglottic folds are close together. These folds are lax. The whole epiglottis is apt to lean backwards towards the entrance to the larynx. On inspiration the soft larynx collapses because of the negative pressure within it, and the epiglottis falls further back and the now even more lax ary-epiglottic folds fall towards each other and vibrate, causing the crowing noise. On expiration the stream of air of increased pressure blows open the larynx and blows apart the ary-epiglottic folds so that expiration is easy and noiseless.

"These babies often have micrognathia, and the effect of the small mandibular arch is to force the tongue backwards, causing laxness of the pharyngoepiglottic folds, and allowing the epiglottis to remain folded and to fall back over the larynx. When the tongue is hooked forward by the finger the crowing inspiration often ceases. As the child grows, the epiglottis becomes less folded, and the aryepiglottic folds lie wider apart; the laryngeal cartilages become firmer so that they do not tend to collapse from the negative pressure of inspiration and the mandible improves in shape." Schwartz (5), however, has pointed out that stridor may or may not occur in infants with the same identical anatomical configuration. He attributed the stridor, when it occurs under these circumstances, to failure of mature integration of the neuromuscular reflexes of the larynx.

Crooks stated that in some instances the arytenoids have flaps of soft tissue on top and during inspiration they may prolapse and slide forward and produce stridor by vibrating in the glottic opening. He has surgically removed this soft tissue with cure of the stridor. He also observed stridor caused by cysts in or near the larynx in four infants, by hemangiomas in the lower part of the larynx in two cases, and a foreign body in the larynx in another infant.

Schwartz (5) has also described what he terms an "exudative stridor," which appears to be associated with an increased mucous secretion of the laryngeal glands. Such excess mucus may result in sudden episodes of vomiting, choking, pallor and collapse. This suggests that some of the cases recorded in the older medical literature as thymic stridor might have belonged in this category. Schwartz stated that this type of stridor suggests an allergic component in the pathogenesis of congenital laryngeal stridor. It is exceedingly interesting that of 30 cases of exudative stridor in infants who are now adults Schwartz found an unusual number of allergic subjects.

Allen and associates (2) have described a form of stridor in infancy associated with apnea and cyanosis which may also be accompanied by loss of consciousness and convulsions. The symptoms of respiratory embarrassment appear to be due to overactive autonomic reflexes rather than to organic obstruction. These cases are uncommon and, as far as the pediatric allergist is concerned, the symptom complex should suggest that the condition is not asthmatic. For details as to the investigation and treatment of such problems

reference is made to the original communication of Allen and associates.

Most of the patients with congenital stridor in my experience have suffered from this because of elongation of the epiglottis. In one instance where the epiglottis was particularly long and flaccid, there was so much respiratory embarrassment that it was necessary to amputate a portion of it. This was attended with complete success. In all the other instances the infants uneventfully outgrew their difficulty within about a year.

Kennedy and New (4), who reviewed thirty cases of congenital stridor admitted to the Mayo Clinic over a period of ten years were able to make a final diagnosis in only thirteen cases; there were eight of congenital relaxation of the larynx and one each of tracheal subglottic diaphragm, laryngospasm, multiple papilloma of the larynx and stridor due to cerebral palsy.

Probably the most interesting case of laryngeal stridor I have ever seen occurred in a two and one-half year old girl who was admitted to the pediatric service of Genesee Hospital with a diagnosis of bronchial asthma. I was able to examine her while she was having an attack of dyspnea. It was obvious that she did not have bronchial asthma but was having respiratory difficulty due to laryngospasm. It was observed at this time that the child had a *Monilia albicans* infection of long standing involving the buccal mucous membranes including the tongue and the finger nails and direct laryngoscopy showed plaques of *Monilia* on the vocal cords. A blood calcium of 4.2 mg. % was reported and phosphorus of 11.2 mg. %, the lowest and highest values respectively yet seen on our pediatric service. The diagnosis, therefore, was laryngospasm due to tetany. This was probably secondary to hypoparathyroidism which for some unknown reason may occur in *Monilia albicans* infection according to Talbot and associates (7). They reported two patients in whom chronic moniliasis preceded the onset of clinical hypoparathyroidism (and incidentally of hypoadrenocorticism) by a matter of months to years. My patient responded nicely to the treatments for relief of the hypoparathyroid tetany but the moniliasis has remained an unsolved problem.

Since, as previously emphasized, the diagnosis of bronchial asthma is a clinical and not a laboratory diagnosis, unless the pa-

tient is having an attack of what the referring physician or the family believes is asthma, a diagnosis cannot be made immediately. If the patient is having an attack, however, it may be possible to make a tentative diagnosis either of bronchial asthma or possible congenital laryngeal stridor at that time. If the infant is not having an attack or in case of doubt it is my custom to make a postnasal smear for eosinophils (see Chapter 28) and do a set of scratch tests, both of which are commonly negative in infants with congenital laryngeal stridor. The patient is then put on routine asthmatic environmental control and an elimination diet with due regard for any positive skin tests which may have been obtained. Symptomatic medications for asthmatic attacks are also prescribed, to be used when the infant has the attacks of stridor for the purpose of observing their effect. If the attacks are uninfluenced by these measures, which will be the case in the infant who suffers from congenital laryngeal stridor, the patient is hospitalized and examined by the laryngoscope and, if this is negative, by the bronchoscope. At such examinations, if no anatomical abnormality is found, smears are made of the secretions to be stained for eosinophils and cultures made for identification of organisms, sensitivity tests and autogenous vaccine for subsequent use if indicated. The infant should also have been studied roentgenographically, including a barium swallow, to rule out a double aortic arch or other intrathoracic abnormality.

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THE DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA (Continued)

ASTHMATIC BRONCHITIS

ASTHMATIC bronchitis is a term applied to paroxysmal attacks of dyspnea which occur particularly in children but which may occur at any age. The attacks are accompanied by the physical signs of asthma including wheezing and evidence of a respiratory infection. It is an important condition in infancy and childhood because it is relatively common and its relationship to bronchial asthma is uncertain in the minds of many. Other terms, synonymous with asthmatic bronchitis, are spastic bronchitis, emphysematous bronchitis and occasionally, capillary bronchitis. Asthmatic bronchitis commonly starts with a coryza; fever is usual; there is poor response to sympathomimetic drugs; nasal smears show a preponderance of neutrophils, and the sedimentation rate is somewhat increased. However, asthmatic bronchitis, particularly as it occurs in children, has been suspected of being of allergic origin because it is so frequently followed by bronchial asthma as the child grows older.

Boesen (1) found that less than 10% of children with asthmatic bronchitis under one year of age later developed asthma. Over the age of one year but without a family history of allergy about 30% did so. In the case of children over three years of age with a positive family history of allergy over 70% ultimately developed bronchial asthma.

It is theoretically possible that true asthmatic bronchitis purely of infectious non-allergic origin may occur. As long ago as 1907, Ingals (5) in doing bronchoscopies in children, noted that the bronchial tubes dilate during inspiration and contract during expiration. This observation has since been confirmed by many others including Jackson (7). Under such circumstances it would appear that obstructive emphysema with expiratory wheezing could occur solely

as a result of edema secondary to infection or other causes, as irritating inhalants. This is probably the mechanism of the wheezing heard so commonly in some respiratory conditions in otherwise normal children, usually thought to be of virus origin. In some epidemics this is very common and, as a rule, these children do not later develop typical asthmatic bronchitis or bronchial asthma. The reason that this type of wheezing and asthmatic bronchitis occurs in children more commonly than in adults may be explained in part by another observation of Ingals that the movements of the bronchi previously mentioned are more marked in children than in adults due to the greater elasticity of the tissues and lesser calcification of the cartilagenous bronchial rings in children as compared with adults.

Rackemann and Edwards (11) state that asthmatic bronchitis is a condition in which colds, in allergic children, cause attacks of wheezing because in theory they lower the threshold of allergic equilibrium sufficiently to allow a slight degree of allergy to become clinically manifest. If the wheeze occurs without colds it means that the child is still in contact with some inhalant to which he is sensitive. If the patient with asthma due to animal danders is out of contact with animals and does not wheeze with his colds, one can assume that he is sensitive to animals alone; but if he does wheeze and he is away from animals then the cause is multiple; he is sensitive to other things at the same time. Rackemann classifies asthmatic bronchitis in the group of allergic diseases.

At this point the question may well be asked, "If asthmatic bronchitis is not an allergic disease and is due merely to a local inflammatory process, why doesn't wheezing occur in practically all pulmonary infections?" To my mind there is a relationship between asthmatic bronchitis and bronchial asthma analogous to the alleged relationship between cardiac asthma and bronchial asthma. Not all persons with cardiac decompensation wheeze. The studies of Swineford and Magruder (12) appear to support the theory first advanced by Rackemann (10) that cardiac asthma is the result of heart failure in an allergic or potentially allergic individual. This is, however, not accepted by Unger (13). The fact that asthmatic bronchitis is in my experience always followed by bronchial asthma, if the child continues to have pulmonary difficulty, would suggest that asthmatic

bronchitis is the form which pulmonary inflammation commonly takes in an allergic or potentially allergic child. Just why this happens, of course, remains to be explained.

The term "asthmatic bronchitis" is useful not only to describe the condition under discussion but is also a term which may be used to soften the blow given the parents when they are told that their child has an allergic lung condition. Persistent attacks of asthmatic bronchitis should be studied and treated in the same manner as bronchial asthma.

FOREIGN BODY IN A BRONCHUS

Some of the most tragic mistakes in the differential diagnosis of bronchial asthma are made because the physician does not realize that the symptoms and physical signs of asthma may be reproduced to an exceedingly misleading extent by the presence of an unsuspected foreign body in a bronchus. This is especially true in infancy and childhood because these patients appear at times to exercise almost diabolical ingenuity in getting unsuspected foreign bodies into their bronchial trees. The diagnosis may almost always be made by a roentgenogram, even in the case of a radio-transparent foreign body, because of the local changes produced by its presence. The roentgenogram must be made with care because if too light, for example, a thin not completely radio-opaque foreign body superimposed over a bone may occasionally escape detection. In case of any reasonable doubt concerning the diagnosis, a bronchoscopy is mandatory. This should be considered an emergency and done without delay. Since the advent of the sulfon compounds and antibiotics the danger of bronchoscopy in competent hands has been greatly reduced. Patients may be started on appropriate sulfon or antibiotic therapy as soon as the diagnosis is suspected and continued after bronchoscopy for at least twenty-four hours or as long as may be indicated by the child's condition. It is also possible that ACTH may prove useful in controlling local reactions to certain foreign bodies, as peanuts, which are sometimes particularly irritating to the bronchial tissue, and thus facilitate their removal (9). According to Jackson (6), only 2 to 4% of foreign bodies in the bronchi are coughed up spontaneously; about 99% can be removed by a competent bronchoscopist; and in 98% complete recovery

without sequela should take place if the foreign body is removed without delay.

The following report is typical of simulation of bronchial asthma by a foreign body in a bronchus:

CASE NO. 5124. This boy was first seen at the age of 16 months. A month previously while playing on the ground he attracted the attention of his mother by coughing. She noticed that he had some dirt on his face and thought that some might possibly have been swallowed or inhaled. The cough continued and wheezing developed shortly thereafter. The family physician diagnosed bronchial asthma complicated by bronchitis. A consultant said the child had bronchitis but not asthma. The boy would occasionally develop a rectal temperature up to 39.5°C. (103°F). Throughout the time of examination the child cried furiously and wheezing could not be distinguished. The findings were normal except for increased markings on fluoroscopy in the left hilar region. Because of the possibility that a foreign body might be present, a roentgenogram was made. The film (Fig. 32) showed a pebble in the left main bronchus and when this was removed the child's symptoms completely disappeared.

FOREIGN BODY IN THE ESOPHAGUS

While it is generally known that a foreign body in a bronchus may produce signs and symptoms leading to a mistaken diagnosis of bronchial asthma, it is not so commonly known that this may also occur under certain conditions when the foreign body is lodged in the esophagus. Lell's (8) experience has been previously noted (see Chapter 28). The literature on this subject was discussed by Fabritius (4) and by Boyd (2), who, in 1951, reviewed 400 cases. Fabritius stated that the typical symptoms of a foreign body in the esophagus are: dysphagia or aphagia, odynphagia, vomiting, dyspnea and cough (as a result of reflex irritation) and secretion overflowing into the larynx or a tracheal fistula. It is possible, however, for large foreign bodies to lodge in the esophagus for a considerable period of time without constant interference with swallowing and with symptoms of air passage involvement as a predominant feature. Fabritius reported two such cases.

The first was a girl one and one-half years of age who was suspected of having swallowed a button. She was hospitalized but



FIG. 32. Boy 16 months of age. Pebble in left main bronchus causing symptoms resembling bronchial asthma.

nothing could be found on clinical or roentgenographic examination. Following this she developed a fever with negative findings and later symptoms suggestive of bronchitis. Bronchopneumonia developed and after she had recovered from this respiratory distress

the rales persisted. Her breathing was asthmatic in character. She vomited on a few occasions but had no difficulty in swallowing. A foreign body in the air passages was suspected and bronchoscopy performed with negative results. Her difficulties continued and some time later a roentgenogram of the chest was reported to show slight compression of the trachea, possibly the result of an enlarged thymus. No evidence of a foreign body was found. Bronchoscopy showed a constriction at the upper part of the trachea with a definite anterior-posterior compression but no other pathological changes. On esophagoscopy a wooden button 23 mm. in diameter was found lying lengthwise in the upper part of the esophagus where it was firmly embedded in granulations on both sides. This button had been lodged in the esophagus for two and one-half months.

The other case was that of a boy one and one-half years old who developed dyspnea. This was particularly noted in connection with meals. He vomited occasionally but appeared to have no difficulty swallowing. Roentgenograms of the chest were negative. It was suspected that the respiratory distress might indicate an allergic condition. He also had an attack of bronchopneumonia. A subsequent roentgenogram was reported to show definite constriction of the trachea as seen in hyperplasia of the thymus. No evidence of a foreign body was observed. Esophagoscopy was performed and a wooden button the same size as in the previous case was found in the upper part of the esophagus in the same position. This had been there for about three months. In both patients examination a week after removal of the button showed that the esophageal wall had healed nicely without evidence of stenosis.

Van der Meulen (14) described a five-year-old child in whose esophagus a ring was lodged for two years without being detected while the diagnosis and picture of the disease varied between asthma, bronchitis and laryngitis. Brown (3) reported a boy, three years old, who, when he was three months of age, was seen to have aspirated or swallowed a small metal washer about the size of a five-cent piece. Nothing was done about this although shortly thereafter the baby began to cough and was taken to a physician to be treated for a "cold." For the next three years he suffered intermittent seizures of coughing, followed by short periods of freedom from cough. During these periods of cough, great difficulty was experienced in feed-

ing any bulky foods. There was no mention in the report of any asthmatic symptoms. The child did fairly well until about three years of age when his cough increased, he became weak, irritable, lost weight and refused to eat. This was eventually diagnosed as probably being due to a mediastinitis secondary to infection from the foreign body lodged in the esophagus. It was removed with the esophagoscope and the post-operative course was uneventful. Boyd (2) reported a case of a foreign body in the esophagus of six years' duration.

One of the most important points which should suggest the possibility of a foreign body in the esophagus in a patient who appears to have intractable asthma, is the fact that this is commonly, altho not invariably, associated with difficulty in swallowing. This, of course, is not characteristic of bronchial asthma. Fabritius (4) emphasized that in looking for foreign bodies in the esophagus roentgenograms should be taken both with and without contrast media and in lateral as well as anterior-posterior positions.

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DIFFERENTIAL DIAGNOSIS OF BRONCHIAL
ASTHMA (Continued)

THE AZYGOS VEIN AND FISSURE

IT MAY occasionally happen that a foreign body is diagnosed in the lung when actually the shadow is of other origin. I once saw such an error made when the suspected shadow was due to an artifact in the cassette which had held the film. However, the most dramatic error I have yet made personally in this direction was mistaking the shadow of the azygos vein for a foreign body. This structure, by virtue of its position, may appear to the uninitiated to be a foreign body in the right upper lung fields. This occurs, according to the late Dr. Nathan Francis* of the Medical Department of the Eastman Kodak Company, who studied a series of 4,600 consecutive chest films, about once in 575 individuals, an incidence of about 0.17 per cent.

The origin of the azygos fissure is explained by the fact that occasionally the migration of the azygos vein in embryonic life from the periphery towards the center of the thorax is not completed. As a result, the vein in its passage to the superior vena cava occupies a cleft extending downwards at a variable distance from the apex to the right lung. It thus divides the right upper lobe into two lobes, the median of which is termed the azygos lobe. This is illustrated in Figure 33. The nature of this structure and its roentgenographic appearance is further illustrated in Figures 34 and 35 (9). Bendick and Wessler (3), of Mount Sinai Hospital in New York, were first to demonstrate by necropsy (Fig. 36) that the above-described shadow, the "inverted comma" in the right upper lobe, actually was caused by the presence of the azygos vein and fissure. This had been postulated but not proven by other roentgenologists previously.

* Personal communication to the author.

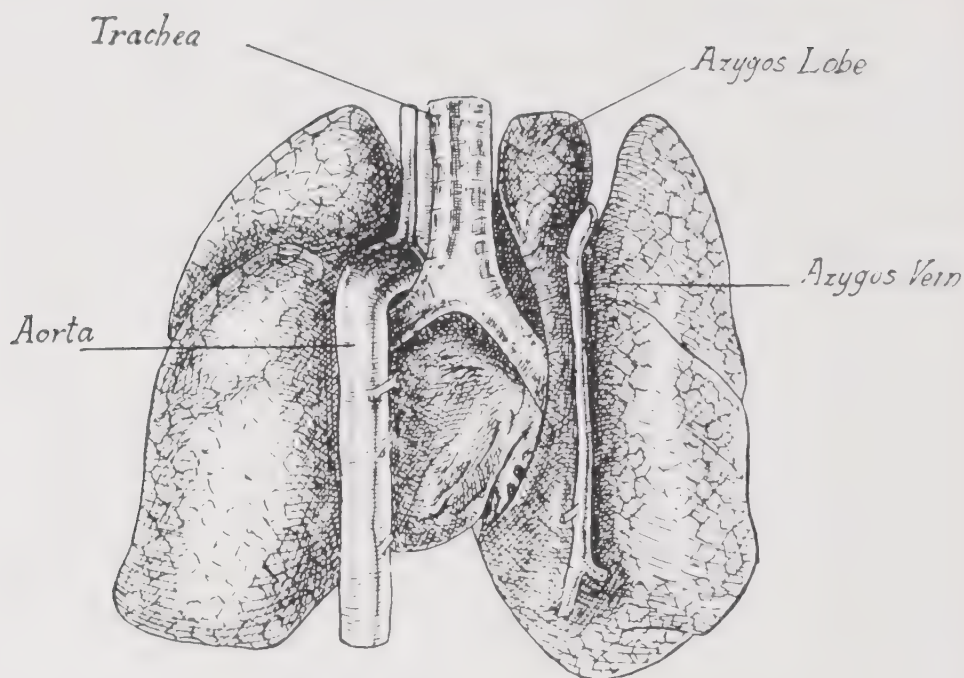
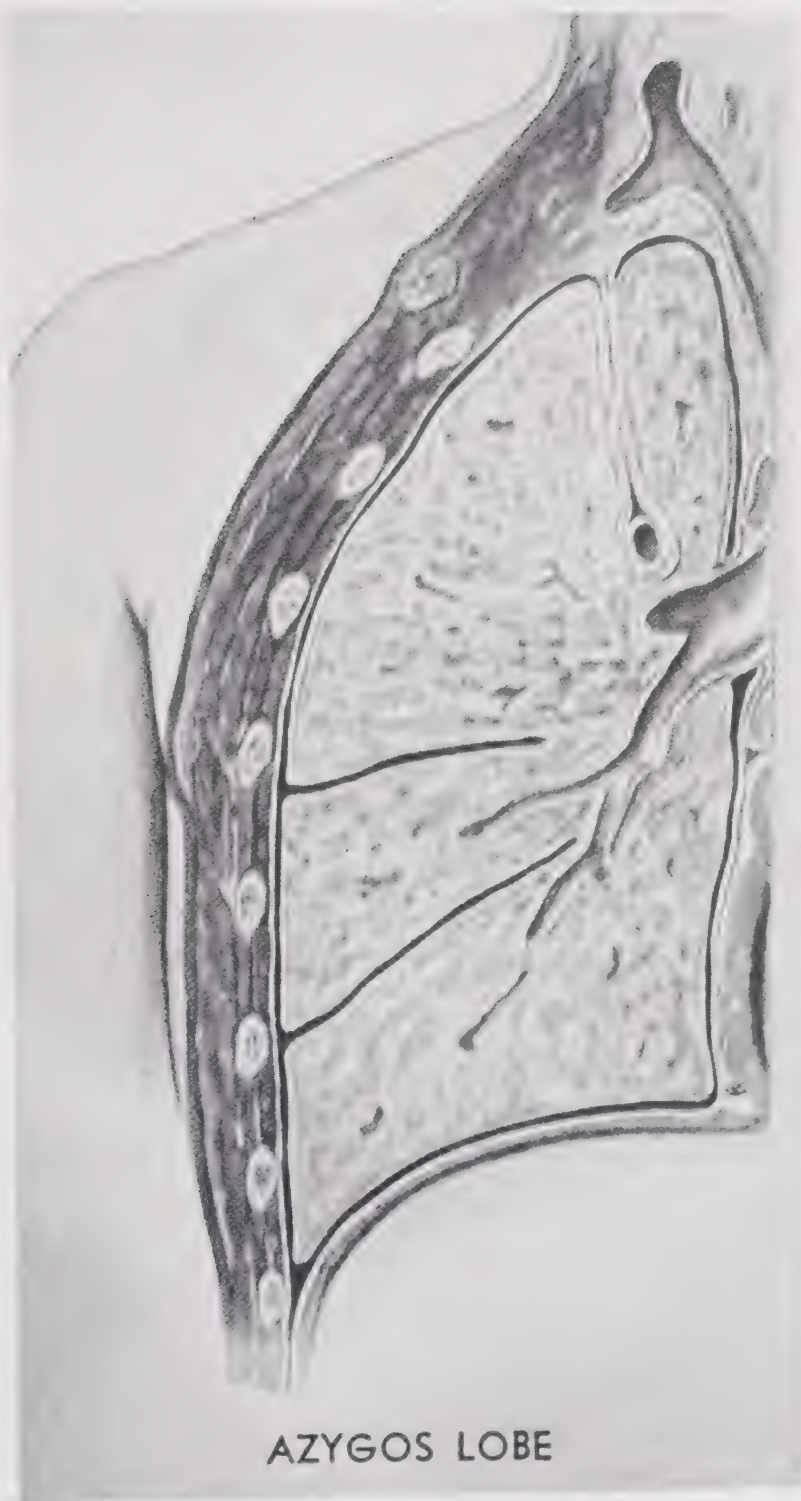


FIG. 33. Sketch of thoracic viscera from behind showing persistent fetal position of the azygos vein with the formation of the azygos lobe. (Modified from Vildes, J., *Acta Universitat Latviensis*, 1924, ix.) From Bendick and Wessler (3).

The case to be reported is one of the most interesting in my experience:

CASE No. 7972. This boy was first seen at the age of six months in a very severe attack of wheezing diagnosed as bronchial asthma. He had been well without preceding evidence of allergic disease until the age of three months when he developed an upper respiratory infection followed by atypical ("virus") pneumonia. Following this the cough persisted and was accompanied by wheezing which had become worse in the preceding five weeks. Just about the time the wheezing became worse a small plastic wheel on a toy car was missing and a three-year-old brother stated that he had put something into the infant's mouth. At the time of this visit the child was fluoroscoped and a small round shadow was noted in the roentgenogram (Fig. 37) in the right upper lobe. A foreign body was suspected, possibly the missing plastic wheel. The child was hospitalized and bronchoscoped but no evidence of a foreign body could be demonstrated. The asthma became worse and another roentgenogram of the chest was made (Fig. 38) in which it could be determined



AZYGOS LOBE

FIG. 34. Frontal section (drawing) illustrating azygos vein, lobe and fissure. Netter (12).



FIG. 35. Typical roentgenogram (drawing) of the shadow cast by the azygos vein and fissure. Netter (12).



FIG. 36. Photograph of lung removed at autopsy from a young child (age not stated) showing small azygos lobe. This is the first instance in which the diagnosis of azygos lobe and fissure made by the roentgenogram was confirmed by autopsy. Bendick and Wessler (3).



FIG. 37. Boy 6 months of age suffering from bronchial asthma. Shadow in right upper lobe mistakenly diagnosed as a foreign body.



FIG. 38. Same case as illustrated in Fig. 37. The shadow in the right upper lobe may now be recognized as that of an azygos vein and fissure.

that a very fine line was present in the upper lobe of the right lung. It proceeded down from the apex to the shadow described above, so that this line, together with the shadow it joined, resembled an "inverted comma." This is typical of the appearance of the azygos fissure and vein as demonstrated by the roentgenogram. The boy definitely had asthmatic breathing but it was not due to a foreign body as suspected. Sometime later, when the boy died because of an intercurrent infection which could not be controlled by the methods then available, the diagnosis of azygos vein, and fissure was confirmed by necropsy.

GENERALIZED OBSTRUCTIVE EMPHYSEMA OF INFANCY (Bronchiolitis or Capillary Bronchitis)

Acute and chronic respiratory disturbances, in which the principal clinical manifestation is an expiratory type of dyspnea associated with generalized emphysema, are not uncommon during the first few years of life. Terms most commonly used to describe this condition are, "bronchiolitis" or "capillary bronchitis." Others are: pneumonitis, interstitial pneumonia, aspiration pneumonia, bronchopneumonia, and asthmatic bronchitis.

According to Pratt (11) this syndrome occurs most frequently in infants three to eighteen months of age. It is characterized by rapid, labored respirations, audible wheezing, prostration, cyanosis, pulmonary emphysema, and signs of exudate in the smaller air passages, leading to obstructive dyspnea and terminal asphyxia. It generally begins with nasal discharge followed by a slight cough and an increased respiratory rate. The breathing becomes noisy and is described as "wheezing" or rattling in the chest. It may be accompanied by diarrhea or vomiting and there is usually moderate fever. As the condition becomes worse breathing becomes more difficult and audible wheezing occurs in about one-third to one-fourth of the patients, a symptom which leads to confusion of this condition with bronchial asthma.

Nelson and Smith (8) stated that clinically there are certain similarities of this syndrome to asthma. However, in contrast to the usual relatively short duration and limited course of the average attack of asthma, even the acute forms of obstructive emphysema in infants tend to persist for a week or so, and often much longer.

Furthermore, while asthma is perhaps the most frequent cause of obstructive emphysema in older children, it is relatively uncommon in the first year or two of life when the conditions discussed characteristically occur. In my own experience, I have at times found it impossible to make a correct differential diagnosis from bronchial asthma except tentatively in retrospect, depending upon the further progress of the child with respect to asthma.

Nelson and Smith (8) described illustrative cases which produce this type of respiratory condition including aspiration of amniotic fluid during birth, fibrocystic disease of the pancreas, atypical bronchial pneumonia, laryngobroncho-bronchitis, miliary tuberculosis, aspiration of zinc stearate powder, and chronic passive congestion secondary to congenital heart disease. It is of considerable importance that such a great variety of different diseases may produce essentially the same clinical syndrome.

Pratt (11) made the interesting observation that allergy or chronic respiratory tract infection is of no more than normal frequency in the families of these patients. However, he did not mention smears of the nasal or pharyngeal mucus for eosinophils, and there was no mention of blood counts with reference to eosinophilia. Roentgenograms show certain characteristic changes (10): Emphysema involves all portions of the lungs, and the emphysematous tissue bulges into the interspaces. There is increase in bronchiovesicular markings and varying degrees of peribronchial infiltration, with small patches of pneumonic consolidation or atelectasis towards the base. There is irregularity of aeration with multiple small areas of emphysema surrounded by normal or partially atelectatic lung tissue. The mediastinum is not displaced. The diaphragm is depressed and the thoracic cage is fixed in a position of extreme inspiration.

A small proportion of these infants, although seriously ill, make a rapid recovery within a day or two. Only rarely does acute bronchiolitis progress into a protracted bronchopneumonia. Such an occurrence would lead one to suspect the presence of some underlying disturbance, such as fibrocystic disease of the pancreas or the aspiration of a foreign body.

The treatment of the disease is symptomatic with the use of the appropriate sulfon and antibiotic drugs, fluids, oxygen, water vapor, etc. Aminophylline intravenously may be successfully used to relieve

the wheezing. (For the dose see Treatment of Bronchial Asthma, Chapter 37.) Walker (13) recommended the use of aqueous ACTH 20 mg. every eight hours for seventy-two hours in most cases. This method of treatment, however, is yet to be evaluated.

FIBROCYSTIC DISEASE OF THE PANCREAS (MUCOVISCIDOSIS)

Andersen (1), in 1938, first described this disease and emphasized its pulmonary aspects. Because it is now realized that this disorder involves many more tissues than that of the pancreas, the more general term of "mucoviscidosis" was introduced by Farber (7) in 1945.

Andersen and diSant'Agnese (2) classified the condition into three main groups: (1) Meconium ileus. In these cases the meconium does not undergo normal pancreatic digestion but persists as a rubbery mass causing death by intestinal obstruction. There is no satisfactory surgical or medical treatment and the patients rarely live longer than a week. (2) A group of cases characterized by failure to gain, even on an adequate diet, in the neonatal period; a large abdomen at birth; hunger; absence of vomiting or diarrhea; intolerance of fat in the diet, and chronic infection of the upper respiratory tract. (3) A group of cases presenting the celiac syndrome (see Chap. 11).

Dickey (6) in reviewing the subject, stated that "in any patient under two years of age with a chronic respiratory infection extending from the tip of the nose to the alveoli, with a negative sputum and a negative tuberculin test, fibrocystic disease of the pancreas should be thought of immediately."

The respiratory symptoms are believed to be due to increased vulnerability of the lung to infection possibly in part because vitamin A is not absorbed, due to failure of absorption of fats which are the usual vehicle of vitamin A. The most common organism found in the lungs is the staphylococcus aureus. There is mild tubular dilation of the bronchi and bronchioles and squamous metaplasia of the bronchial epithelium. The bronchi are plugged with greenish-gray, mucopurulent material. It is particularly because of these pathological changes that the symptoms of asthmatic bronchitis or asthma are produced. This occasionally leads to subjecting children with this disease to allergic study.

The chief laboratory aids in making the diagnosis of fibrocystic disease of the pancreas are: Absence of satisfactory response to sympathomimetic drugs as regards the cough and wheezing; absence of eosinophilia in the bronchial secretion; failure to absorb glucose properly as indicated by the glucose tolerance curve; poor absorption of vitamin A as indicated by the vitamin A tolerance test (4, 5), and diminution or absence of pancreatic enzymes on duodenal drainage.

The following case, reported through the courtesy of Dr. Herbert C. Soule, Jr., is a typical example of this disease.

The patient was the third child of normal parents. The family history was interesting in that the child had an older sister with ragweed pollen asthma and a brother who had died on the eleventh day after birth from a meconium ileus secondary to fibrocystic disease of the pancreas. Another sister had developed normally. Starting at the age of three weeks the patient's breathing was observed to be noisy on exertion and asthma was suspected. A roentgenogram of the chest was reported normal. A consulting bronchoscopist suspected a slight stenosis of the larynx. The boy did rather well, however, until about the age of five months when his weight was 7.3 kg. (16 pounds). Abnormal stools had never been observed. At this time he developed a troublesome cough and considerable dyspnea and asthmatic bronchitis was considered. Epinephrine was injected and appeared to give a little relief. Skin tests done by the consulting allergist were negative. Experimental changes in diet did not help.

At the age of seven months the boy's condition was so serious that he was admitted to the hospital where he died twelve days later. The necropsy revealed subacute bronchitis, bronchiolitis, bronchopneumonia, and fibrocystic disease of the pancreas.

DUST BRONCHITIS

This type of bronchitis, previously noted in the "Dust Bowl" area, was described in children by Toomey and Petersilge (12). It is due to the inhalation of finely pulverized dust. In their cases, it was inhaled by children playing on a large clay field during a spell of warm weather. The principal symptom was an explosive, intractable, non-productive cough, which was exaggerated by excitement, deep breathing, or lying on the back. The temperature often reached

38.2 C. (101 F.) but soon became normal after putting the child to bed. Whistling noises were heard in the lungs with loud rhonchi at the bases. Roentgenograms showed only soft, patchy mottling with increased markings along the course of the bronchi. Treatment was symptomatic with sedatives and expectorant cough mixtures.

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CONGENITAL LOBAR EMPHYSEMA

This disease has been recognized with increasing frequency during the past few years. DeBord and Sibilsky (1), who reported a case of unknown etiology in a two-month-old infant in 1954, stated that theirs was the forty-first case recorded in the literature. Korngold and Baker (3) have since added two more. These authors stated that the etiology of lobar emphysema as determined by the examination of the specimens removed surgically or at necropsy are as follows, the numbers in parentheses indicating the number of such cases reported:

1. Infolding of the bronchial mucosa and decrease in the size of the cartilage (2).
2. Ductus arteriosus compressing a bronchus (2).
3. Inflammatory process obstructing a secondary bronchus (1).
4. Absence of the anterior mediastinum (1).
5. Slightly aneurysmal vein in bronchus (1).
6. Unusually small bronchus lacking in cartilage (1).
7. Deficiency in bronchial cartilage (1).
8. Bronchus with soft collapsible walls and fewer than normal cartilaginous rings (1).
9. No etiological factors found (12).

In the two cases reported by Korngold and Baker the patients' condition was considered too poor for surgery. They aspirated air from the emphysematous lobes using a No. 18 gauge needle inserted to a depth of one inch and treated the complicating tension pneumothorax by reaspiration of the accumulated air in the thorax. This was not found necessary after twenty-four hours as the affected lobe expanded to normal size. The authors postulated that in their cases a bronchus might have been kinked by an over distended emphysematous lobe and that retained viscid secretions augmented the bronchial obstruction in the new born. They recommended that this procedure be tried when the condition is newly established and reversible and may be of value when surgery is indicated to improve a poor risk. In the past this disease, unoperated, has carried with it a mortality of almost 100 per cent, whereas almost no mortality has attended the operation of lobectomy, even at this early age. Fischer, Potts, and Hollinger (2) summarized the clinical course of congenital lobar emphysema as follows: An infant or young child previously well is noted to suffer dyspnea or cyanosis or both, unrelated to a febrile pulmonary inflammatory process. Symptoms progress and respond poorly to conservative therapy. On physical examination there is hyperresonance and diminished breath sounds of one side of the thorax or of the lobar area, with displacement of the heart and mediastinum away from the hyperresonant side. The roentgenogram shows a large area of localized radiotranslucence with shift of the heart and mediastinum away from the affected area. The diaphragm on that side is likely to be depressed. The area of radiolucency may be noted to be in the distribution of a single lobe.

but frequently the lobe is so overdilated that it is difficult to recognize it as such. Partial atelectasis of other lung tissue of the same side or the other side may be present. The radiolucent area can be diagnosed as emphysema rather than pneumothorax or single or multiple cysts, because lung markings are present throughout the entire area. Bronchoscopy and bronchography are important and are of value mainly in excluding intraluminal causes of emphysema, the most important of which is a foreign body. Exploratory thoracotomy reveals a greatly overdilated emphysematous lobe which does not collapse upon opening the chest. The uninvolved lung tissue can be expanded by the anesthetist. The child makes a quick recovery following lobectomy, and returns to a normal life without disability. There have been no instances of recurrence of symptoms, and no other lobe has developed this syndrome after removal of the first affected lobe.

Shaw (4) stated that the most important point in the history is the development of a wheeze in the absence of evidence of a respiratory infection. While any chest that wheezes is almost certainly to be suspected of harboring asthma, Shaw's report did not mention this in the differential diagnosis nor is the possibility of mistaking this disease for asthma mentioned in most publications. However, Shaw* stated that the child reported by him, who was four years old at the time of surgery, had been considered as an asthmatic and had had the usual studies and treatment for this disease. It is therefore important for the pediatric allergist to consider this condition in the differential diagnosis of wheezing in early life although it appears evident that lobar emphysema can be ruled out with reasonable ease if only the condition is kept in mind.

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* Personal communication to the author.

THE DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA (Continued)

THYMIC ASTHMA

THYMIC asthma is a condition which was frequently mentioned in medical literature many years ago. It referred to a paroxysmal type of dyspnea believed to be due to pressure on the trachea from an enlarged thymus gland. This was first described by Kopp (5) in 1830 and hence is occasionally called "Kopp's asthma." Whether or not this condition actually existed was much debated and greatly doubted. Following the development of aseptic surgery about 1890, when it became possible to remove the thymus surgically, evidence was established by Olivier (7) that Kopp's original contention was occasionally correct. In the great majority of instances, however, the dyspnea eventually proved to be due to some cause other than enlargement of the thymus gland. Because of this and particularly because of the report of the Status Lymphaticus Investigation Committee in England in 1931 (11), most authorities felt that thymic enlargement sufficient to cause symptoms did not exist. However, the development of the study of clinical allergy has caused a revival of interest in the study of the thymus as related to dyspnea, the most important contributions being those of Aldrich (1), Waldbott (9), and Carr (2).

Aldrich (1) stated that in his own experience there were many patients with an expiratory wheeze indistinguishable by physical signs from ordinary bronchial asthma and considered as true bronchial asthma for weeks or months until the true diagnosis of enlarged thymus was made. Aldrich believed that thymic asthma may be related to true bronchial asthma in that both may be considered manifestations of vagotonia. Radiation over the thymus appeared effective in relieving the symptoms whether or not the gland was enlarged.

Carr (2) described the pathological findings in what he termed "status thymico-asthmaticus." He stated that the clinical course of these cases is distinguished with difficulty from true bronchial asthma except for the single but very important fact that the status thymico-asthmaticus group shows no beneficial response to the injection of epinephrine. These patients die of asphyxia, and at necropsy more or less enlargement of the thymus is found. He correlated the pathological findings in these patients with those of Waldbott (9) in two cases of death from asthma in infancy. Waldbott was struck by the similarity in findings in these cases to those previously described in so-called thymic death and felt that this condition and death from allergic shock might be equivalent. In Carr's cases the same type of anatomical and cytological abnormalities as that noted by Waldbott was found.

Littleton and associates (6), as a result of their detailed investigation of the thymus problem, concluded that children subject to repeated bouts of stridor, cough, and cyanosis and who often appear to have benefited dramatically from radiation therapy, probably have an underlying low grade or recurrent tracheobronchitis that is favorably affected by the treatment.

In recent years, however, post-mortem studies have demonstrated that most instances of so-called "thymic death" are due to peracute infections or to other causes which have nothing intrinsically to do with the thymus gland. The pendulum has now swung in the direction where it is popular to attribute no mortality or morbidity to the thymic gland rather than attributing all unknown causes of death to the thymus. However, it is desirable to keep an open mind with regard to possible disorders of a gland whose function is not yet known. The thymus is said to be the most hydrolabile organ in the body and it is easy to understand how, because of its position just below the thoracic inlet, a sudden marked edema of allergic or other origin could result in pressure on vital structures sufficient to cause death. Because the edema might disappear by the time the patient came to necropsy, the true cause of death might not be suspected. There is no organ of the body which does not at times show disease or abnormal function and it is unlikely that the thymus is an exception to this rule.

MISCELLANEOUS CONDITIONS

Pressure of anomalous vessels on the trachea, usually in the form of rings around the trachea, may produce an asthmatic type of stridor. A detailed description of these vascular anomalies has been published by Gross and Neuhauser (4). It is important to remember that these lesions, though congenital, may not cause symptoms until some time after birth. Carson and Goodfriend (3) reported one such infant where "wheezing" was not noticed until the age of seven months. In most instances the stridor is inspiratory in nature. Welsh and Munro (10), however, saw a child with expiratory dyspnea caused by an aberrant pulmonary artery.

Pressure on the carina, particularly by enlarged nodes or other tumors, has also produced dyspnea suggestive of bronchial asthma. Peshkin and Fineman (8) over a four-year period in their asthma clinic found three children with this difficulty who had, however, been referred because of "asthma." It was determined that their symptoms were due to enlarged tuberculous tracheobronchial nodes. This characteristically occurs before the second year.

One of the most remarkable cases that has come to my attention was a five-year-old boy seen by Dr. George A. Peck* of Salt Lake City. The patient had been studied and treated for asthma but no roentgenographic studies had been made of the chest. Films taken by Dr. Peck showed large echinococcus cysts of both lungs which produced symptoms of asthma caused by pressure on the bronchi.

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THE DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA (Continued)

CARDIAC ASTHMA

THE TERM “cardiac asthma” refers to severe attacks of dyspnea simulating asthma which occur in some individuals with cardiac failure from any cause, particularly left ventricular failure and tachycardia in cases of marked mitral stenosis. Attacks most commonly occur suddenly at night when the patient is sound asleep in the reclining position. Attacks may also occur on unusual efforts when awake. Unlike bronchial asthma, the injection of epinephrine aggravates the symptoms, and also unlike bronchial asthma, the best treatment is the injection of morphine.

Swineford and Magruder (12) have given their support to the theory first advanced by Rackemann (8) that cardiac asthma is a form which heart failure of various types may take in an allergic or potentially allergic individual. Unger (13), on the contrary, believes that there is no particular relationship between allergy and cardiac asthma. I have been unable to find in the literature any reports of this condition in infancy and childhood. White (14) states that the youngest patients he has ever seen with cardiac asthma were eighteen and twenty-two years of age, respectively. He suggests that the reason the condition does not occur in the lower age groups is that although heart failure does occur in this group, both ventricles commonly fail together so that there is no unilateral strain on the right ventricle.

Dr. Samuel W. Clausen called my attention to the records of two children observed by him at the Strong Memorial Hospital, both of whom suffered typical attacks of cardiac asthma, a diagnosis reached after careful study and consultation with a cardiologist. One of these occurred in a girl eleven years of age as a complication of subacute hemorrhagic nephritis. She died of cardiac failure two days after the

attack of cardiac asthma. The other patient was a boy, twelve years of age, who had attacks of cardiac asthma complicating acute hemorrhagic nephritis. He apparently made a complete recovery and was discharged from the hospital. The family left Rochester not long afterwards, and his subsequent fate is unknown.

CONGENITAL HEART DISEASE

While cardiac asthma is exceedingly rare in pediatric practice, recurrent infections of the lungs may occur rather commonly in congenital heart disease. Dr. Helen B. Taussig* stated that any child with a large heart and poor circulation with or without pulmonary hypertension is subject to repeated chest infections as any upper respiratory infection tends to descend to the lower respiratory tract if the circulation is poor and the patient's resistance is low. Such infections occur in the large ductus arteriosus, with or without pulmonary hypertension; in auricular septal defects; in high ventricular septal defects; in the Eisenmenger group; in children with primary pulmonary hypertension the many and severe respiratory infections are the bane of their existence. Dr. Alexander S. Nadas* also wrote that there can be no doubt at all that patients with large left to right shunts have increased severe respiratory infections, even pneumonia and congenital heart disease should be considered in the differential diagnosis of children with frequent attacks of pneumonia. In some patients this is so striking that the diagnosis of fibrocystic disease of the pancreas has been seriously entertained in a few instances. Sub-endocardial sclerosis or endocardial fibroelastosis of severe degree is also accompanied rather frequently by intractable pneumonitis.

SIGHING DYSPNEA

As a nosological entity this condition was first described by Maytum and Willius (6) in 1934 and again by Maytum (5) in 1939. It is important to the allergist because, although not accompanied by wheezing, it is often confused with bronchial asthma and referred to the allergist for study. It is a functional disorder of respiration and is not caused by organic disease.

If seen during an attack, diagnosis is easy. Although the patient

* Personal communication to the author.

has dyspnea which may vary greatly in severity, there is no wheezing or cough and no evidence of obstruction to respiration. Physical examination is usually normal, but other conditions such as asthma and cardiac disease may co-exist and must be properly evaluated. If not seen during an attack the history is characteristic. The patient complains of "shortness of breath," or "inability to take a deep breath," or "I cannot fill my lungs and I get frightened," etc. In bad attacks the patient may have a very severe dyspnea and appear acutely ill. If the attack is prolonged, tetany may develop. The treatment is psychotherapy.

Prince (7) has seen two cases of sighing dyspnea in children but the only complete report in the literature on children is that of Silberberg (10) who described a case in a boy thirteen years of age. Overwork and strain had made this patient dislike school although he was a bright boy. He became much interested in making a miniature motor car but this was beyond his capacity and caused a sense of frustration. One day in class he found himself gasping for breath, trying to fill his lungs. He continued to take long sighs for about half an hour; then his hands felt paralyzed. He developed parasesthesias in his hands, patellae, and about his trunk, and also had a peculiar sensation in his head. These were symptoms of tetany due to hyperventilation. He remained at home for two days. On returning to school a similar attack occurred which alarmed his teacher. The physical examination shortly thereafter was negative and Silberberg regarded the boy as manifesting a hyperventilation syndrome. Explanation and reassurance were given and the boy remained well.

POST-ENCEPHALITIC HYPERPNEA

Maytum (4) has reviewed the brief literature on this subject. He states that respiratory disturbances following encephalitis may be responsible for paroxysmal attacks of noisy breathing which may be mistaken for asthma. This occurs occasionally in adults but most often in children, in whom there is often an associated change in behavior and personality. The respiratory symptoms consist of a series of deep, noisy respirations followed by a period of apnea during which the patient stretches and goes through a series of stereotyped

actions. True dyspnea and the characteristic pulmonary signs of asthma are absent, and there is a history of encephalitis preceding the respiratory symptoms in most cases.

AYERZA'S DISEASE

This is a very rare, chronic pulmonary disease accompanied by wheezing and was first described by Dr. Abel Ayerza of Buenos Aires in 1901. The best description in English is given by Smith (11). Its etiology is obscure but is probably due to chronic bronchopulmonary changes. In its later stage the disease is characterized by five cardinal signs: (1) dyspnea; (2) polycythemia; (3) chronic cyanosis, which is said to be the first sign which should make one suspect that the patient does not have bronchial asthma; (4) prominence of the pulmonary cone with right ventricular hypertrophy, and (5) right ventricular preponderance by the electrocardiogram. From one to twenty-five years may be required for the complete development of this syndrome.

Death commonly occurs from cardiac failure. The findings at necropsy are sufficiently constant to be diagnostic: (1) typical manifestations of death due to cardiac failure are present; (2) the lungs show the effect of chronic bronchitis and emphysema, and (3) dilatation and sclerosis of the pulmonary arteries are the striking and unusual features.

The following is a brief abstract of the case reported by Smith.

The patient was a thirteen-year-old white girl who was seen because of the following complaints: asthmatic attacks of eight years' duration; cyanosis of six years' duration, and headaches of four years' duration. The child's past personal history and her family history were negative for allergy. The condition started at the age of four and one-half years when she began to have attacks of croup and bronchitis, perennial but worse in the winter. She was studied by two competent allergists with completely negative findings and failure to obtain relief. Cyanosis had started insidiously at the age of seven years, and its progress was steady. Headaches were attributed to sinusitis, and, in the four years previous to being seen, the child had been in Tucson, Arizona, where she showed slight improvement. Studies for tuberculosis were completely negative. Shortly before being seen the child's dyspnea had increased and the cough became

very productive, mucopurulent in nature and frequently blood streaked.

On physical examination she was a fairly tall, dyspneic, asthenic girl presenting the typical appearance of a child with long-standing asthma. The most striking feature was a generalized cyanosis. Auscultation of the lungs gave the findings typical of chronic asthma. The heart sounds were normal. There was no clubbing of the fingers or toes. The blood pressure was normal. The blood findings were as follows: red blood cells 6.1; haemoglobin 130 per cent Sahli, and white blood cells 6,200 with 48 per cent polymorphonuclear leukocytes, 42 per cent lymphocytes and 10 per cent eosinophils. The Kahn test was negative. A roentgenogram showed accentuated bronchovesicular markings throughout, an unusually prominent pulmonic cone, widening of the intercostal spaces and depression of the diaphragm.

On bronchoscopy the mucous membranes of the pharynx and tracheobronchial tree were deeply purple, thin and friable. The trachea and both bronchi contained a large amount of exceedingly tenacious material. There was no gross obstruction in the airway. Each branch bronchus was in normal position and its lumen filled with a frothy white secretion. There was no evidence of the anterior-posterior collapse of the bronchi usually seen in a far advanced asthmatic.

The patient died not long after having been studied of an acute respiratory infection, probably pneumonia. Necropsy was not performed.

BRONCHOTETANY

This is a rare condition which may occur in children suffering from tetany when the disease affects the bronchial musculature. It was first described by Lederer (3) in 1913. He reported six cases in infants, all of which were fatal. The clinical symptoms consist of dyspnea, which may be severe, wheezing, use of the accessory muscles of respiration, dilatation of the alae nasi, and suprasternal and lateral costal margin retractions. Dullness may be percussed in some pulmonary areas with hyperresonance due to compensatory emphysema elsewhere. Bronchial breathing may be heard in some areas with various types of rales in other areas. A high fever may lead to the diagnosis of pneumonia. The roentgenographic diagnosis

is commonly atelectasis. Rietschel (9) mentioned a case in an infant with recovery. Curschmann (2) reported a subacute case in a thirty-two-year-old man who had been repeatedly diagnosed as having bronchial asthma. The patient was easily cured by the usual methods of treating tetany. He recommended that every young adult diagnosed as having bronchial asthma of unknown etiology be also studied for tetany.

In bronchotetany the hypodermic administration of epinephrine is contraindicated, as the symptoms are made worse thereby. The administration of calcium, particularly intravenously, is followed by brilliant results. It is my opinion that the possibility exists that the beneficial results reported occasionally following the intravenous administration of calcium in asthma, which lead to its widespread use for this purpose many years ago, were probably obtained in patients whose pulmonary manifestations were the result of tetany rather than of bronchial asthma.

THE ALLERGIC COUGH

No discussion of the problem of the differential diagnosis of bronchial asthma in infancy and childhood would be complete without mention of the symptom of cough. Persistent cough is a very common problem in childhood and for a discussion of this general subject reference is made to the work of Bell (1). From the standpoint of allergy, cough may be regarded as a pre-asthmatic symptom because it often happens that a persistent cough in an allergic child for which no adequate cause can be discovered eventually develops into bronchial asthma. When such a cough occurs the problem of differential diagnosis becomes acute. The two principal types of cough which may be confused with the asthmatic cough are those of pertussis and those of nasal or paranasal origin. The latter cough is commonly secondary to allergic nasal mucous membranes.

There is a certain similarity in the origin of the coughs of asthma and of pertussis in that both may result from the plugging of small air passages by mucus and the cough is commonly relieved when the mucus is dislodged by the act of coughing. In general the asthmatic cough and that of pertussis may be differentiated by the following procedures:

1. Therapeutic test: The cough of pertussis does not respond to sympathomimetic drugs; the allergic cough commonly does.

2. Absence of eosinophilia in the nasal and bronchial secretions in pertussis and their presence in cough of allergic origin.

3. A high leucocyte count with a relative lymphocytosis is often characteristic of pertussis.

4. A positive culture for *H. pertussis* may commonly be obtained in pertussis. This is especially important because of the present routine practice of immunization against pertussis with highly effective vaccines which leads to situations, for example, where a child may cough briefly for a few days only without whooping and it would not be known that he had pertussis were it not for a positive culture.

5. No wheezing in pertussis on forced expiration as commonly occurs with asthmatic coughs, even in the absence of wheezing on normal respiration.

6. In pertussis a typical whoop develops after about three weeks.

It must, of course, not be forgotten that pertussis may complicate asthma so that a child may suffer from the symptoms of both.

The nasal cough presents a special problem because allergic nasal mucous membranes so often accompany bronchial asthma, particularly in children. Very commonly in children with bronchial asthma there is obtained a history of nasal difficulty, as perennial allergic rhinitis, which started at the same time as the asthma. Both the nasal cough and the asthmatic cough are commonly worse at night, the asthmatic cough for unknown reasons. The cough of nasal origin occurs more frequently at night because in children the ethmoid sinuses, which are those most commonly involved, in the prone position drain back into the throat causing cough from irritation by post-nasal drip. This type of cough may also occur when the child changes his position during the day, for example, when he lies down on the examining table for skin tests to be done on his chest. The nasal cough may also be due to dripping from hypertrophied and infected adenoids, from the recurrent lymphadenoid tissue which so commonly recurs following adenoidectomy in allergic children (which will shortly be discussed in detail), and polypoid degeneration of the posterior tips, particularly of the inferior turbinates, which occurs in children though not nearly as commonly as in adults.

Roentgenograms of the sinuses are often of considerable assistance in determining edema or infection of the paranasal sinuses and the recurrence of lymphadenoid tissue in the roof of the pharynx.

However, it is always well to accompany these procedures by direct inspection by the nasopharyngoscope. Too few nose and throat specialists are willing to spend the time necessary to examine the nose carefully and shrink down the mucous membranes fully in a frightened and uncooperative child. It takes real skill to do a posterior rhinopharyngoscopy, without which the diagnosis is often missed, in such a child. The patient goes from one nose and throat specialist to another and from one allergist to another without relief. It is well for the pediatric allergist to train, so to speak, one capable nose and throat specialist of his acquaintance to carefully examine the nasal passages of infants and children. For this purpose a specialist just starting practice with unlimited time at his disposal and a desire to make good, will prove most satisfactory. His efforts will be well rewarded by the development of a technique which will enable the accurate diagnosis of lesions in infants and children often missed by his older and less patient colleagues.

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COMPLICATIONS OF BRONCHIAL ASTHMA

EMPHYSEMA

THE MOST common complication of bronchial asthma at any age is emphysema. This does not result in permanent changes in the thoracic cage unless the patient is in status asthmaticus for a very long period. In children, because of the factors of growth, uncalcified costochondrium and the relative softness of the ribs themselves, a characteristic type of deformity of the thorax may appear after long continued asthma which Bock (2) has very aptly designated as "asthmatic pseudo-rickets." In true rickets, however, the upper transverse diameter of the thorax is greatly narrowed whereas in asthmatic pseudo-rickets the upper transverse diameter is greatly enlarged. This gives, roughly speaking, in both instances a pear-like appearance to the trunk. In asthmatic pseudo-rickets the larger portion of the pear corresponds to the emphysematous thorax while in true rickets the pear appears inverted with the larger portion of the pear corresponding to the commonly distended abdomen below the flaring costal margins and the typically small chest of rickets. In both instances the basic mechanism is the same, i.e., the effect of the muscle pull of respiration under abnormal conditions. In rickets the primary factor is the softness of the thoracic cage itself responding to the muscle pull; in asthmatic pseudo-rickets plus emphysema the primary factor is the abnormal muscle pull on the thoracic cage. Even in the presence of this deformity, if the asthma is relieved in early childhood, the thoracic cage tends gradually to assume the normal shape.

ATELECTASIS AND MASSIVE COLLAPSE OF THE LUNGS

A certain amount of atelectasis probably always accompanies an asthmatic attack. Most of the time, because of the spread of the asthmatic rales throughout the chest these localized areas cannot be diagnosed. They are also commonly too small to be diagnosed on percussion. Occasionally enough mucus may be formed so as to com-

pletely obstruct a bronchus and cause atelectasis of an entire lobe or, as it is commonly termed, "massive collapse." Such a case is illustrated in Figure 39. This girl was hospitalized in an exceedingly severe attack of asthma. A film of her chest showed complete collapse of one lung. Bronchoscopic aspiration was considered but the child coughed up the mucous plug and lung expanded. Ratner (17)



FIG. 39. Massive collapse of the right lung complicating asthma in a five and one-half year old girl.

has reported dramatic success in such instances by the use of ipecac to produce vomiting. The act of vomiting appears to milk out the trachea, producing what Reinberg (18) described as "tracheal vomiting." It is also possible, according to Gunn (13) that a certain element of bronchial peristalsis plays a part in this. However, if the child does not spontaneously cough up the mucous plug in massive atelectasis or if it cannot be dislodged by vomiting then bronchoscopic aspiration is indicated.

AIR IN THE EXTRAPULMONARY SPACES

Air in the extrapulmonary spaces is, according to Hansel (14) an uncommon complication of bronchial asthma. A detailed discussion of the mechanism whereby this may happen is given by Derbes *et al.* (8). In infants and children this is very rare. Field (10) reported an asthmatic girl a little over four years of age who when first seen had subcutaneous emphysema extending around the neck on the face and over the chest, abdomen, and thighs. The roentgenogram showed collapse of the left lower lobe. Ten days later she developed a right sided pneumothorax with massive collapse of the left lung and partial collapse of the right upper lobe. However, she eventually made a good recovery.

A case of mediastinal and subcutaneous emphysema was reported from the Children's Memorial Hospital of Chicago (4) in a girl five years of age with asthma. The diagnosis was made by the roentgenogram. The possibility of death due to cardiac tamponade was discussed. If this is threatened the air in the mediastinum must be released surgically by needle puncture, dissection through the neck or splitting the sternum.

Kahn and Rouse (15), in 1951, stated that of the seventy-three cases of spontaneous mediastinal emphysema reported in the literature up to that time, only twenty-eight were due to asthma and of these only one, an adult, was fatal. They reported a five-year-old boy who, during an asthmatic attack of moderate intensity, developed considerable swelling of the anterior thoracic wall and the neck and the cheeks bilaterally. The subcutaneous areas showed marked crepitation. The roentgenogram indicated widespread mediastinal emphysema, emphysema about the pericardium, and some tracheal compression.

Figure 40 illustrates some of the features of this case. There was no pain at any time. The child was put at rest and given small doses of epinephrine (3 minims) every three hours. The swelling and crepitation began to clear after about twelve hours, progressively improving until both were gone in about five days. Asthmatic symptoms, which were very minimal, were controlled from the beginning and at the end of twenty-four hours the epinephrine was discontinued.

Spontaneous pneumothorax without interstitial emphysema as a

complication of bronchial asthma, although reported in adults (8), so far as I am aware has not occurred in children. The youngest case I have discovered was that of Davidson and Brock (6) in a sixteen-year-old girl.

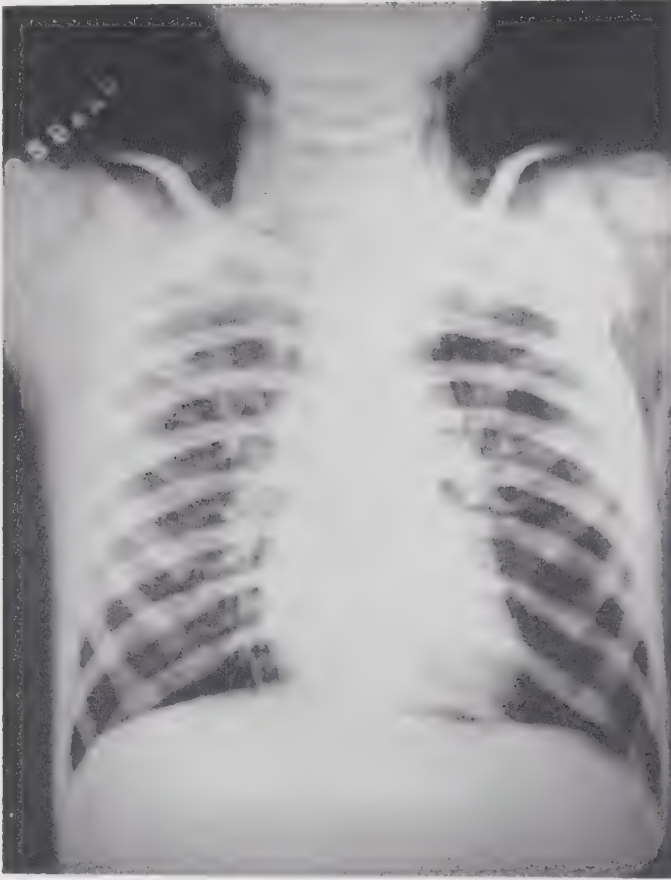


FIG. 40. Roentgenogram of a five year old boy showing widespread mediastinal emphysema, emphysema extending to the neck and face, emphysema about the pericardium and some tracheal compression. From Kahn and Rouse (15).

HEART DISEASE AND ASTHMA

Invariably every parent of a child who has repeated attacks of bronchial asthma, asks the question, "Doctor, will this damage my child's heart?" The answer to this has been given by Derbes and Engelhardt (7). They studied the heart size and contour of twelve asthmatic children ranging in age from five to fourteen years whose asthma varied in duration from one to nine years and could find no

abnormality on fluoroscopy or on roentgenograms. They also studied (9) a series of seventeen children with an average age of 9.3 years; the youngest being five and the oldest fourteen years. The average duration of the asthma was 4.7 years with a minimum duration of fourteen months and a maximum of nine years. Detailed studies of the electrocardiograms were reported as normal. The authors felt that uncomplicated bronchial asthma in childhood is not a factor in heart disease. They state that this does not militate against the production of heart disease subsequent to pulmonary fibrosis, emphysema, bronchiectasis or other pulmonary complications seen in a chronic asthmatic state.

TUBERCULOSIS AND ASTHMA

Mothers of asthmatic children, especially if the children are underweight, frequently ask about the possibility of the development of pulmonary tuberculosis in their child. Black (1) stated that he has seen few adults and no children in whom tuberculosis and asthma were co-existent. In practically every instance in adults in whom both conditions were present it was possible to prove that tuberculosis antedated the asthma. Tocker and Davidson (19) have reviewed the literature of the subject and reported studies of their own. They concluded that the incidence of tuberculosis in individuals with asthma approximates the incidence of these illnesses in the normal population. They felt that their findings refuted the reports of earlier writers that: (1) tuberculosis and asthma are mutually exclusive; (2) tuberculosis predisposes to asthma, and (3) there is a common specific form of asthma based on an allergy to tubercule bacilli. E. A. Brown (3) in a later study which also summarized the literature and his own experience, stated that groups of patients with true bronchial asthma show the same tendency to tuberculosis as does the general population and groups of patients with pulmonary tuberculosis show the same incidence of true bronchial asthma as does the general population. Thus the parent of an asthmatic child need have no more concern than any other parent as far as tuberculosis is concerned.

SPONTANEOUS FRACTURE OF THE RIBS

This has been reported in adults by Waldbott (21) and by Ginsburg (12). The fractures usually result from violent coughing in which unusual muscular strain is applied to the ribs. Localized pain

is a characteristic feature. I have never experienced this in children nor have I ever seen any reports of this condition in childhood.

DEATH FROM ASTHMA

Death from bronchial asthma in childhood does occur but is now much less common than formerly due to better methods of controlling dehydration, the use of antibiotics and sulfon drugs and, in some instances, of the new drugs, ACTH and cortisone.

A death in a twenty-two-month-old boy, probably from infection, was reported from the Children's Memorial Hospital of Chicago (5). Pedrera (16) reported the death in a thirteen-month-old boy with asthma the mechanism of which he did not believe was satisfactorily explained but felt that the dehydration and disturbances of acid base equilibrium may have played a large part. Unger (20) recorded five deaths from bronchial asthma including the case of one colored girl a year old who was known to have had asthma since the age of three months. The necropsy showed pulmonary infection.

Gay (11) reviewed the literature of the pathology of asthma and to this added a series of twenty-four patients at the Johns Hopkins Hospital who died after a clinical diagnosis of bronchial asthma had been reported either as a primary or secondary cause of death. In this series there were three infants. One was a boy who died at the age of six months with asthma complicated by infection. Another was a girl twenty-seven months of age in whom the anatomical diagnoses were: bronchial asthma; obstruction of the bronchi by mucus; cardiac dilatation and hypertrophy, and emphysema. The cardiac findings are very interesting in view of a possible correlation between bronchial asthma and heart disease as discussed above. The third patient was a twenty-month-old girl who died during the first attack of asthma which had lasted for only two days. The anatomical diagnoses were: bronchial asthma with partial obstruction of many bronchioles; foci of atelectasis and pulmonary edema, and bronchiectasis. From these three cases Gay drew several lessons: 1) That the prognosis for acutely ill asthmatic children is always serious. Hospitalization is preferable as frequently dehydration requires intravenous fluids. 2) Even small doses of morphine should be avoided (the second child had a small dose of morphine with apparent relief at first but suddenly stopped breathing and died in a state of emphy-

sema). 3) Bronchoscopic aspiration of mucus is indicated even in infancy but it is impossible to dislodge mucus from distant bronchi.

I should like to add also that these cases, since they are always apparently accompanied by infection, should be early and vigorously treated with appropriate antibiotics and sulfon compounds. I now also always use ACTH or cortisone in such patients. The deaths reported by Gay occurred before such treatment was possible.

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THE RELATIONSHIP OF THE TONSILS AND ADENOIDS TO BRONCHIAL ASTHMA

ONE OF the early students of this problem was Peshkin (9) who, in 1927 in a study of 100 asthmatic children, concluded that tonsillectomy aggravated the asthma in 3 per cent. Only one patient appeared to improve as the result of the operation and this improvement was only temporary.

Bullen (1), in 1931, in a report on 300 patients presenting nasal or pulmonary symptoms of allergy on whom tonsillectomies had been done and of 300 similar patients whose tonsils had not been removed, concluded that the good results and the failures from treatment were almost identical in the two groups. In a ten-year follow-up study the incidence of nasal or pulmonary manifestations of allergy in 1000 school children whose tonsils had been removed at the age of five or six years, and of 1000 similar children who had been advised to have their tonsils removed but had not done so, a slightly greater number of the children whose tonsils had been removed developed allergic symptoms than of the children who had retained their tonsils. Bullen concluded that tonsillectomy does not, with rare exceptions, improve the results of treatment of nasal or pulmonary manifestations of allergy. He also stated that nasal or pulmonary manifestations of allergy are as liable to occur in an individual whose tonsils have been removed as in one who retains his tonsils.

Clein (2), in 1949, pointed out that when an adenotonsillectomy is performed for the relief of such symptoms as nasal obstruction and discharge and recurrent "colds," the results are often unsatisfactory because the underlying difficulty is due to unrecognized allergy. Sobel (10), in 1953, reviewed the whole problem and reported the results of her own studies. She concluded that *the indications for adenotonsillectomy should be the same for allergic and non-allergic patients*. In other words, allergy *per se* cannot be considered an indication for tonsillectomy. With this I am in full agree-

ment. I should also like to add that I have, over the years, developed the following further impressions which have thus far not been subjected to statistical analysis in my own practice (7):

(1) A child with upper respiratory allergy of any type, particularly pollinosis, who has an adenotonsillectomy during the pollinating season is more likely to develop bronchial asthma or have exacerbations of previous bronchial asthma than if the operation is done during the seasons of non-pollination. Sobel (10) also advises (and I concur), that in allergic children this operation should be done during a pollen-free period.

(2) Any child who has to have the tonsils or adenoids or both removed more than once is an allergic child. While not stating this in exactly the same words, Clein (2) confirmed this observation, at least in part, by stating that recurrence of lymphadenoid tissue in tonsillar fossae occurs in 27 per cent of allergic children as compared with 3 per cent non-allergic children.

(3) Practically all children who require the removal of the tonsils or adenoids or both at the age of three years or less are allergic children.

RECURRENT LYMPHADENOID TISSUE IN THE NASOPHARYNX

In 1938, Crowe and associates (3, 5), reported the use of radiation in the treatment of lymphoid hyperplasia of the nasopharynx. These investigators were primarily interested in the treatment and prevention of deafness. Their studies revealed the wide distribution of lymphoid tissue in the nasopharynx in addition to the pharyngeal tonsil or adenoid. Lymphoid tissue is found even in the membranous portion of the Eustachian tube, often more prominently at the pharyngeal end where the collection of lymphoid follicles is known as the "tubal tonsil." Lymphoid follicles are also widely distributed throughout the mucous membrane of the nasopharynx.

Crowe and his associates observed that during childhood lymphoid tissue in the throat reacts to infection by increasing in size and spreading to where the mucous membrane is normally free from it. It often happens that, after removal of the tonsils and adenoids in children and in some adults, numerous nodules of lymphoid tissue, often present but not particularly prominent before operation,

appear on the lateral and posterior walls of the pharynx. This condition is called "granular pharyngitis." It is easily seen on the posterior wall of the oral pharynx. When it occurs in the oral pharynx, it is, as a rule, seen even more extensively in the nasopharynx. When these follicles obstruct the internal ostia of the Eustachian tubes, high tone impairment of hearing may result.

These investigators found that more than 75 per cent of children who had an adenotonsillectomy had a marked post-operative recurrence of adenoid tissue in the nasopharynx. This was not due to poor surgery in the original operation but to a tendency of lymphoid tissue to recur in the mucous membranes. This tissue cannot be entirely removed by any operation because it is not practical to denude the nasopharynx of the mucous membrane. Repeated operations are useless and radiation is the only satisfactory method of treatment. Even with radiation, some recurrence of lymphoid tissue may occasionally take place.

Ward (11), working in Crowe's clinic in 1943, observed that among the hundreds of children being treated for the prevention of deafness, there were a number with typical asthma. Many were sensitive to the usual inhalants but failed to respond to hypo-sensitization and avoidance of dietary and environmental allergens. Nasopharyngoscopic examination revealed hypertrophied adenoids and lymphoid tissue scattered throughout the nasopharynx. In most of these children, the attacks of asthma were preceded by coryza. Following radiation therapy, the frequency and severity of attacks were, in many cases, reduced and in some instances, the asthmatic attacks were even eliminated. This chance observation led to a careful nasopharyngoscopic study in a series of thirty-four patients who had previously undergone adenotonsillectomy, with reference to the lymphoid tissue which had recurred in the nasopharynx after operation. These children were treated with 2 gm. min. of exposure to radon gas on each side of the nasopharynx once each month for an average of four treatments. In twenty-three of the thirty-two cases the lymphoid tissue completely disappeared. Reactions to the radon treatment consisted of sneezing and nasal discharge and occasionally asthmatic attacks. It was estimated that 68 per cent of the children obtained from total to 50 per cent relief, while 32 per cent obtained no relief. The mechanism by which relief is obtained is not com-

pletely understood. Perhaps it is chiefly due to the elimination of focal infection in the lymphatic follicles which act as a trigger mechanism. Other factors may be reduction of post-nasal secretion, definite change in the bacterial flora and possibly a change in the threshold of absorption of allergens from the nasopharyngeal tissue after the lymphoid tissues disappeared.

Crowe and Walzi (4) state that the action of radiation is confined to the cells and germinal centers of the lymphatic follicles. A few days after radiation the cells show chromatolysis and fragmentation of the nuclei. Since the life span of the mature lymphocyte is only a few weeks, the mass of tissue gradually shrinks because there is no replacement of the damaged germinal centers.

Gay (6), reporting on radiation therapy, stated that the child who has frequent colds associated with asthmatic bronchitis will often get dramatic relief, in conjunction with specific desensitization therapy where indicated. Cough due to post nasal drip was occasionally dramatically relieved. He emphasized the great importance of nasopharyngeal study.

Mueller and Flake (8), reported a series of forty-one children who had been observed for periods of six months to four years, with 85 per cent of the children followed for two years or more. These patients were carefully selected by allergists and otolaryngologists using the following criteria: (1) a history of asthma of over two years' duration associated with respiratory infections; (2) failure to obtain satisfactory results with other measures for infectious asthma or by other methods of allergic management, and (3) the finding of hypertrophied lymphoid tissue in the nasopharynx, or evidence of infection or both.

The children were treated either by x-ray or radium irradiation. In the radium treated group each patient received direct application of radium salt in the standard 50 mg. Monel metal applicator to each side of the nasopharynx, each application being of 100 mg. for eight to ten minutes. Three treatments were given on to each side of the nasopharynx four weeks apart. This type of treatment requires cooperation and is not practical in children under five years of age. In the group treated with x-rays each received two treatments, varying from one to three weeks apart, with 100 r for eight to ten minutes. Untoward effects from the radium treatments were

minimal and consisted of some local discomfort at the time and slight increase in nasal stuffiness for twelve to twenty-four hours. Reaction to x-ray treatment consisted of occasional swelling and soreness of the parotid glands for twenty-four to forty-eight hours, but there is a theoretical possibility that too much radiation might cause damage to centers of ossification of the skull of the young child. Both radium and roentgen methods of treatment appeared equally efficacious.

The authors state that improvement was observed for periods from six months to four years in 80 per cent of those treated with no particular tendency to recurrence. Good results were chiefly dependent upon reduction of frequency and severity of respiratory infections. No explanation was found for the failures of treatments.

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SYMPTOMATIC TREATMENT OF BRONCHIAL ASTHMA

CERTAINLY one of the most common precipitating factors of an asthmatic attack at any age is an acute upper respiratory infection. The frequency with which asthmatic attacks are associated with infection has led to the belief by some that infection is the principal, if not the only cause, of asthma. However, there is another explanation which appears more logical in the light of what is known about allergy in general. The allergic individual who has asthma suffers from a chronic, clinical or sub-clinical edema of the membranes of the respiratory tract or a potential edema which may develop into clinical edema on exposure to particular allergens. Because of this, these membranes are, like all other edematous tissues, particularly subject to infection. It is further possible that the infection lowers, in some way, the allergic resistance of the mucous membranes so that allergens which would not normally cause asthma may do so. This results in a kind of vicious circle: The mucous membrane rendered edematous by certain allergens is readily infected. This infection further lowers the allergic resistance of the membranes so that the same allergens may cause further difficulty, or other allergens which would not normally cause asthma may do so. It is also evident that, if the primary edema is severe enough, asthma may occur without any infection whatsoever as a contributory factor.

The prevention and treatment of infections is a highly necessary procedure, but should not lead one away from a constant search for basic allergic causes, i.e., the allergens to which the mucous membrane is susceptible. It is possible that in some instances the offending allergen may be the infectious agent itself, but our knowledge concerning this is very incomplete. Occasionally what appears to be the onset of an acute upper respiratory infection may be only the expression of an allergic reaction involving the membranes of the

upper respiratory tract and unrelated, in any way, to an infectious agent.

If the upper respiratory infection, or "cold," can be prevented or aborted, the asthmatic attack may often be prevented. This single important observation has led to a systematic approach to the problem of preventing or minimizing asthmatic attacks following apparent upper respiratory infections, and was first presented by the author in 1946 (9). This method is equally applicable to adults and children. Suggested measures for this purpose, besides, of course, the complete study of the patient from the standpoint of allergy, are as follows:

(1) It may, in some instances, be possible to prevent or abort the "cold," either of infectious or allergic origin, by the administration of an antihistaminic drug immediately at the very first sign or "aura" of a cold. This procedure, which was first advocated by Brewster (5), appears to be highly successful in some instances. The older child can often recognize almost the very moment of the beginning of a coryza. This may be a scratchy sensation in the throat or a feeling of malaise. The mother of younger children can often detect the onset of a coryza by changes in the behavior or appearance of the child. She may note listlessness or irritability, or some change in the expression of the child. The most unusual "aura" which I have encountered to date was frequency of micturition in one child. However, the first symptom which the mother commonly notes is the onset of sneezing or cough. It is then important to discover how long an interval *in terms of hours or days* there usually is between the onset of these symptoms and the onset of asthma.

It is highly important that the antihistaminic be started without delay, because the longer the delay (even an hour or two is important), the less satisfactory will be the results. A teaspoon of Elixir of Benadryl (10 mg.) or of Elixir of Pyribenzamine (30 mg. of the citrate equivalent to 20 mg. of the hydrochloride), or larger doses of the capsules or tablets of these or other suitable antihistaminics, depending upon the age of the child, should be given every four hours when awake. The antihistaminics should not be continued more than twenty-four hours if they have a drying effect on the secretions. If the mother is in doubt as to whether or not her child is coming down with a "cold," she had best start the antihistaminic anyway as a prophylactic measure. However, she soon learns by experience when the drug really should be started.

At the present time, the routine use of antihistaminic drugs for the prevention of colds has been largely discredited, as indicated by Burrage's (6) very complete review. However, there may be a difference between using these drugs to prevent coryza in allergic individuals and in non-allergic individuals. Middleton and Rider (16) found these drugs helped allergic as compared with non-allergic individuals in a relatively small series. Much further study needs to be done to clarify this point.

(2) There are a certain number of patients wherein the upper respiratory infection with consequent asthma cannot be aborted by the use of antihistaminic drugs and other nonspecific measures outlined below. In such instances, the employment of an antibiotic or sulfon drug, started along with the antihistaminic at the very first "aura" of the cold, will further assist in preventing the development of an upper respiratory infection. This by no means signifies that the drug acts upon the virus of the cold. I am in agreement with those who feel that the mechanism of a common cold is somewhat as follows: Resistance of the respiratory mucous membrane is lowered either by allergy, as in the cases under consideration, or by changes in temperature, humidity, and probably many other causes, so that the virus of the common cold can enter the membranes and start to grow. This is responsible for the initial stage of the cold with the watery discharge and sneezing, perhaps due, in part, to the liberation of histamine or histamine-like substances in the tissues which may be neutralized in this initial stage to some extent by antihistaminics. The nasal membranes are rendered more permeable by this reaction to the virus and are then invaded by secondary organisms which proliferate, causing the next stages of the cold with thickening of the secretions and the invasion of the tissues and secretions with polymorphonuclear neutrophils, causing a purulent nasal discharge. The antibiotic or sulfon drug, if administered immediately at the beginning of the cold, appears, in many instances, to check this secondary invasion of pyogenic organisms.

For a time, penicillin aerosol, in doses of 75,000 to 100,000 units or more three or four times a day, was administered until the danger of an attack had passed. The parents were taught how to administer the aerosol at home using the modified bicycle pump (8).*

* This pump, together with a suitable vaporizer, is marketed by the DeVilbiss Company as the hand pump vaporizer combination No. 740.

with the development of effective methods of administering penicillin and other antibiotics in relatively large doses orally or, if necessary, parenterally, the use of aerosol for this purpose has been largely discontinued.

(3) In a limited number of cases, patients with frequent, recurrent, upper respiratory infections, followed by asthma, may be greatly relieved by the continuous administration of an antibiotic or sulfon drug in the same manner as employed for the prophylaxis of rheumatic fever. If oral penicillin is used, the dose is 200,000 to 250,000 units, twice a day, on an empty stomach, commonly one-half hour to one hour before meals and at bed time (4). If a sulfon drug is used, chiefly because it is less expensive, we employ the dose advocated by Baldwin (1). She gave children weighing less than 50 kg. (110 lb.) 0.5 gm. of sulfadiazine in the morning, and those weighing more took the same additional dose at bed time. With these doses, blood levels were found to range between 1 and 3.5 mg. per cent, and the drug is administered throughout the year or during the period when the patient suffers with the recurrent, upper respiratory infections. The blood and urine must be carefully watched and if the white count drops below 4,000 the drug discontinued. It may often be resumed again without difficulty.

Bowen (3) has stressed the value of gamma globulin injections in preventing asthma in children who have recurrent upper respiratory infections. He advocates injections of 5 cc. each, once every thirty days. This procedure is employed even if the blood gamma globulin level is normal. I have not used this routinely, but in one six-year-old girl, who in the days before steroid therapy, would come repeatedly into the hospital cyanotic and almost moribund with asthma, the blood gamma globulin was found to be the lowest ever reported in the hospital. She did well after the injection of gamma globulin and never had to have a hospital admission thereafter, at least until the time of this writing, a period of about six years. In a small series of other infants and children who had severe asthmatic attacks following repeated upper respiratory infections, the blood gamma globulin was consistently normal or slightly elevated, probably due to the infection. The subject of agammaglobulinemia is further discussed in Chapter 43.

ROUTINE MANAGEMENT OF ASTHMATIC ATTACKS FOLLOWING ACUTE UPPER RESPIRATORY INFECTIONS

The measures about to be discussed are indicated in Table XI, which is an example of the kind of typewritten directions given to the parents of suitable asthmatic patients at the time of the first visit. It must be emphasized again that, for these procedures to be successful, they must be started between the onset of the very first sign

TABLE XI

ROUTINE MANAGEMENT OF ASTHMATIC ATTACKS FOLLOWING ACUTE UPPER RESPIRATORY INFECTIONS

Name of Patient Date Height Weight

I. *IMMEDIATELY*, at the very first sign of an impending upper respiratory infection, which in this case is, proceed as follows in order to prevent or modify the attack. This must be done immediately, as a delay of even an hour or more may mitigate against the best results:

Put the patient to bed and give the following medications every four hours for the first twenty-four hours, when the patient is awake, and thereafter as necessary:

1. An antihistaminic*
2. A cough medication*
3. A vasoconstricting nose drop*

The bedroom should be as free from house dust as possible (see accompanying direction sheet) and from the odors of fresh paint, burning leaves, tobacco smoke, cooking odors, flowers, perfume, etc.

II. Insert an aminophylline suppository* every twelve hours, by the clock, until the danger of an asthmatic attack is passed.

III. If the above measures fail to prevent an asthmatic attack, then at the onset of the next upper respiratory infection, in addition to the above measures, you will be given directions for the administration of an antibiotic.

IV. Study carefully the accompanying pamphlet, "Care of the Child with Chronic Asthma," and do your best to make a personal application.

V. Return for skin tests on these dates:

* Prescription or sample given.

of an impending upper respiratory infection and the onset of the asthma. This time lag may vary from an hour or less to several days, and the earlier this routine is instituted the more likely it is to be successful. A delay of even an hour or more may, in some instances, mitigate against the best results. In general, the routine is as follows:

I. BED REST

While this does not always appear to be practical with older children, it is, nevertheless, the best procedure. This protects from aggravating factors, as exercise and sudden changes in temperature. If the patient is a potentially allergic child, or if he has had asthmatic attacks before, environmental control should have been instituted,

at least in his bedroom. This should be as free as possible from house dust, wool, feathers and other epidermoids, pyrethrum containing insecticides, and from strong odors as fresh paint, burning leaves, the dust from dried leaves, tobacco, tobacco smoke, cooking odors, perfume, kerosene, gasoline, moth balls, fresh cut flowers, etc. These are routine precautions which should be taken regardless of the history or skin tests.

The following medications are started simultaneously and continued every four hours the first twenty-four hours, while the patient is awake, and thereafter as necessary:

- (a) An antihistamine in suitable doses.
- (b) A cough mixture.
- (c) Nose drops.

II. COUGH MIXTURES

The following cough mixtures have been found highly satisfactory. That found by experience to be the best for the child should be used. It is a practical point to number cough mixtures, like ointments and other medications, so that when the mother telephones or comes in the medication used can be easily identified. These mixtures are for the average child of three years of age. The doses of the various ingredients may be varied according to their effect upon the child and the age and weight of the child.

	Codeine sulphate	0.25 gr iv*
	Ephedrine sulphate	0.40 gr vj*
	Glycerin	10.00 dr ij
Label: Cough	Syr. hydriodic acid	
Mixture No. 1.	Syr. cherry, N.F.	
	aa qs ad	120.00 Oz iv
Sig: 1 tsp. q 3-4 h prn for cough.		

If syrup of cherry is not available, as is commonly the case in the smaller drug stores, soda fountain syrup of cherry, which is essentially the same thing, may be used in its place. The pharmacist should be given permission to do this on the prescription. I prefer

* If the patient is allergic to ephedrine, then propadrine hydrochloride may often be used with success in equivalent or slightly larger doses. If sensitive to codeine or other opium derivatives one may try Romilar Hydrobromide (Roche), a non-narcotic preparation (the dextrorotary form of 3-methoxy-N-methylmorphinian hydrobromide) of which 10 mg. (1/6 grain) is said to be approximately equivalent to 15 mg. (1/4 grain) of codeine.

this form of syrup of cherry to the more commonly used syrup of wild cherry (*Syrupus Pruni Virginianae*) because most children accept it more readily.

For a more expectorant effect without particularly changing the taste of the mixture, fluid extract of ipecac, 0.20 to 0.30 cc. (3 to 5 minims), may be added. *It must be remembered that the fluid extract of ipecac is about sixteen times as strong as the more commonly used syrup of ipecac.* Occasionally an asthmatic attack may be checked by ipecac alone, a rather common procedure in folk medicine which has been particularly advocated by Ratner (20). The drug is given for the purpose of producing vomiting, which is often followed by the relief of asthma. The dose is 5 drops of the syrup of ipecac for infants one year of age or less, with one additional drop for each succeeding year (11). It is repeated every fifteen minutes until the child vomits or until three or four doses have been given.

Another satisfactory cough medicine for a child of the same age is:

Label: Cough	Dihydrocodeinone bitartrate*	0.065	gr j
Mixture No. 2	Ephedrine sulphate	0.400	gr vj
	Benylin expectorant† qs ad	120.000	Oz iv

Sig: 1 tsp. q 3-4 h prn for cough.

III. NOSE DROPS

Four or five drops of a preparation containing a vasoconstricting agent should be used several times a day, preferably just before meals so that if the child vomits after the medication the meal will not be lost and the child can breathe easier and therefore eat better during meal times. Drops are also instilled some time later in the evening and again during the night if the child is awake. They should not be used more often than every four hours. Before instillation of the drops, the child should blow the mucus out of his nose, if possible. If too young to blow his nose, the ingenious procedure

* The adult dose is 5 mg. every four hours as necessary; children in proportion.

† This preparation (Parke, Davis and Company) contains 5 per cent alcohol and has a raspberry flavor. The active ingredients are:

Benadryl hydrochloride	0.08	1¼ gr.
Ammonium chloride	0.8	12 gr.
Sodium citrate	0.325	5 gr.
Chloroform	0.12	2 gr.
Menthol	0.006	0.1 gr.

devised by Landau (15), which consists of using a soft rubber ear syringe with the tip trimmed to fit the nostril, is exceedingly useful for aspirating the mucus from the nasal passages of infants and young children.*

One of the most common errors in the administration of nose drops is failure to have the patient in the correct position, which was first described by Proetz (19). The child should be in the supine position with the head, supported by the mother, extended back over the edge of the bed so that the external auditory meatus and the point of the chin are in the same horizontal plane. Generally speaking, when the head is in this position the nostrils will point straight upwards at the ceiling. The opening of the sphenoid sinus will then be at the most dependent position of the nasal chamber. The drops, after instillation, will not run backwards over the roof of the palate into the mouth, as they do when instilled in the usual manner, but will run downwards over the septum and turbinates to the roof of the pharynx, shrinking down the ostia of the various sinuses and permitting better drainage and ventilation. If the physician has any doubts regarding the great superiority of this method, he should try it on himself when he has nasal congestion and be convinced. The head is held in this position thirty to sixty seconds after instillation of the drops.

I originally used the following formula† devised in 1925 (9) for use in the out-patient department of the Sarah Morris Hospital for Children of the Michael Reese Hospital in Chicago, Illinois, and still find it highly satisfactory:

Ephedrine sulphate	1½ %
Dextrose	10
Chlorbutanol	½
Distilled water	qs

The ephedrine is used as the vasoconstrictor. I have rarely observed it to cause irritability and insomnia in young infants, as described by Greene and Greenspan (14), which could not be easily controlled by mild sedation. The dextrose in twice isotonic strength was added because of its dehydrating effect. It is of interest that the use of

* A similar satisfactory device is now marketed by the Becton, Dickenson Company.

† Marketed under the trade name, S.U.G. No. 15 Nose Drops.

"sugar water" in the nose is an old Germanic folk medication which may possibly be effective because of its hypertonicity or because of its effect upon the bacterial flora of the nose. The chlorbutanol was added as a preservative. The efficacy of this preparation is indirectly attested by the numerous proprietary glucose and ephedrine preparations with a similar formula which have since appeared.

Besides ephedrine, a number of other satisfactory vasoconstrictors are now available. These include Neosynephrine $\frac{1}{4}$ per cent (Winthrop-Stearns), Propadrine $1\frac{1}{2}$ percent (Sharpe & Dohme), and Privine 0.05 per cent (Ciba).

Privine nose drops, used in 0.05 per cent solutions for infants and children and in 0.1 per cent solution for older individuals is probably the most effective vasoconstricting nose drop available. However, this preparation must be used with great care because, if used in excess, a type of reaction to the drops suggestive of an allergic reaction may occur. This is characterized by marked nasal obstruction relieved only momentarily by the further administration of Privine. When this happens, the only satisfactory treatment is to take the patient off of the medication and control the resulting discomfort by symptomatic medication until the effect of the Privine wears off.

The principal pharmacologic action of Privine is to elevate the blood pressure by peripheral vasoconstriction. It also causes cortical stimulation, followed by depression, affecting the basal centers somewhat similar to phenobarbital poisoning. Fortunately, this happens but rarely. In cases of severe nasal congestion not satisfactorily relieved by the other types of vasoconstricting nose drops mentioned above, I do not hesitate to use Privine twice a day, preferably at bed time and again four hours or more later if awake and needed, and have never had any difficulties when the drops were used in this manner.

Another useful nose drop is Alconefrin* which contains phenylephrine (neosynephrine hydrochloride, Winthrop-Stearns) in amounts varying from $\frac{1}{8}$ to $\frac{1}{2}$ per cent and benzalconium chloride (Winthrop-Stearns) as an antiseptic and wetting agent, as the active ingredients in a saline solution buffered to nasal tonicity.

Epinephrine is now rarely used as a nose drop because the vaso-

* Alcon Laboratories, Fort Worth, Texas.

constriction it produces is more temporary than that produced by the above agents, and the vasodilation following its use is more marked. Neosilvol and argyrol have very little effect insofar as vasoconstriction is concerned. Their value in the nose for antiseptics is questionable and their prolonged use may result in argyria. The various sulfon preparations in nose drops are also of questionable value.

Menthol should never be used in nose drops for infants and children because of its irritating and toxic effects in this age group. Oily nose drops should never be used because of their tendency to produce lipoid pneumonia, especially in infants and children.

Penicillin nose drops are of very definite value in nasal infections in infants and children. Disagreeable experiences due to sensitization have not been experienced in this age group. However, it is more logical, in order to avoid the theoretical possibility of such sensitization, to use nose drops containing other antibiotics not commonly used orally or parenterally,* but I have found no sulfon and no other antibiotic nose drop to be as satisfactory as penicillin. However, ultimately, other equally effective antibiotic nose drops will doubtless be developed. A practical, simple prescription for penicillin nose drops is as follows:

One soluble tablet of penicillin	50,000 units
Ephedrine sulphate	0.16 gr. 2½
Normal saline qs ad	16.0 oz. ½

If the nose is so completely obstructed by swollen mucous membrane that the drops cannot penerate through to the nasopharynx, the following maneuvers may sometimes help:

(1) The patient lies on one side for ten or fifteen minutes. The uppermost side of the nose will then sometimes open up and the drops should be immediately instilled into that side. The position of the patient is reversed and the process repeated.

(2) A hot bath or shower will more frequently accomplish the same purpose.

IV. STEAM INHALATIONS

These are particularly useful in dry climates or in the winter when the air is dry in cold climates. Steam is irritating to some children, and in such cases should not be used. Medications, especially menthol, should not be added to the steam. Prigal (18) has, however, re-

* As Bacidrin, Upjohn.

ported considerable success by the administration of aminophylline and other drugs, and has devised an apparatus for that purpose. The general use of this procedure awaits confirmation by other investigators.

V. ORAL ADMINISTRATION OF EPHEDRINE

If, in spite of the above measures, the child starts wheezing, ephedrine sulphate or hydrochloride by mouth, in doses of 15 to 50 mg. ($\frac{1}{4}$ to $\frac{3}{4}$ grain), may be used. This reinforces the ephedrine of the cough mixture and will sometimes check the wheezing. It may be necessary to counteract the stimulating effects of the ephedrine by means of a sedative. This may be given at the same time as ephedrine. A small amount of aminophylline, 0.05 to 0.1 gm. ($\frac{3}{4}$ to $1\frac{1}{2}$ grains), may be given orally at the same time, along with the ephedrine and the sedative. Many commercial preparations of tablets are available containing combinations of all three, i.e., ephedrine, aminophylline, and a sedative. Some of these preparations are enteric coated and may be given at bed time with the uncoated preparation to take advantage of the delayed action due to the special coating.

VI. AMINOPHYLLINE SUPPOSITORIES

Aminophylline suppositories were introduced by Dees (7) in 1943 and represent a significant advance in the symptomatic treatment of bronchial asthma. Chapter 37 should be consulted for a discussion of the dosage of aminophylline and of the untoward reactions which may sometimes follow its use. Occasionally a patient will complain of itching or burning from an aminophylline suppository. This may usually be overcome by lubricating the suppository lightly with a water soluble anesthetic ointment. In older individuals the suppository may at times produce a contact proctitis. I have not yet experienced this difficulty in children.

Instead of administering aminophylline as a suppository the drug may also be given rectally by injecting the required dose taken from an ampule used for intravenous or intramuscular administration or a solution prepared by dissolving the required dose of aminophylline powder in water.

The patient threatened with an asthmatic attack should be given a suppository at night and in the morning as a routine measure until the danger of the attack is past. Should asthma occur, the supposi-

tories may be used in the treatment of an active attack and given every six hours. There are a number of very good preparatory preparations of aminophylline suppositories. Some are prepared with sedatives, and, unless the child is sensitive to these drugs, are often somewhat more helpful than the aminophylline alone because of the sedative effect. Most of the suppositories now on the market are not made with cocoa butter so that they may be freely used in patients who are sensitive to chocolate.

If aminophylline suppositories are not available, the powder may be dissolved in warm water and inserted through a catheter (2), or the contents of an ampule of aminophylline, usually containing 0.25 gm. ($3\frac{3}{4}$ grains per 10 cc.) may be administered in the desired dosage. The action of the solution is somewhat more rapid than the action of the suppository. The dose of the drug is the same as indicated above for the suppository, usually 0.25 gm. or less to 0.50 gm., depending upon the size of the child.

VII. INHALATION OF EPINEPHRINE AEROSOL 1/100

Inhalation of epinephrine aerosol 1/100 for the relief of asthma was the first introduced by Graeser and Rowe (13). Should the child now have asthma which is not relieved by the foregoing measures, this procedure is often highly effective. Some children as young as three years may be taught this effectively, but it is not commonly successful before the age of five or six years. It is midway in effectiveness between aminophylline administered rectally and the hypodermic injection of epinephrine. It is important to be sure that the instrument used is not mechanically defective. A DeVilbiss No. 40 vaporizer has been found satisfactory and is much less expensive than some others in common use. After administration of the aerosol, it is advisable for the patient to gargle, or, if too young for this, to swallow a little water, in order to prevent irritation of the throat or stomach. Overdosage of the aerosol must be avoided by not using more than three or four inhalations at a treatment, depending upon the efficiency of the vaporizer.

VIII. EPINEPHRINE 1/1000 BY HYPODERMIC INJECTION

If, in spite of the above measures, the asthmatic attack continues, recourse should be had without delay to the hypodermic injection of epinephrine 1/1000 as the quickest and most effective method of

stopping the attack. *It should be mandatory that someone in the family of an asthmatic child be able to carry out this procedure.* Besides the obvious advantages for the child, the parents are usually impressed by the argument that, if by this means they avoid even one house call by a physician, it will more than pay the cost of the hypodermic syringe, needles and medication.

The two most common errors in this procedure are:

1. Too long a delay between the onset of otherwise unrelieved asthma and the hypodermic administration of epinephrine. This is generally due to the reluctance of the parents to call a physician at some unreasonable hour if they do not know how to give a hypodermic injection themselves, or, if they do know how, their reluctance to do so, or their hope that the child will be able to fight off the attack without it. It must be emphasized to the parents that the earlier the hypodermic is administered the more effective it is and the less the child will suffer.

2. Improper dosage of epinephrine. The tendency is to use too large a dose. The proper dose is the minimum which will accomplish the desired effect because this dose will also minimize the disagreeable side reactions. An infant of four to six months may be started on 0.15 cc. (2 minims). An average child of three years of age would be relieved of a moderately severe attack by 0.25 cc. ($3\frac{3}{4}$ minims). It may be necessary to repeat the dose several times at intervals of fifteen to twenty minutes, gradually increasing the amount, if no result is obtained, until the child gets relief or gives the usual evidence of being refractory to the drug (pallor, cold sweat, tremors, patchy cyanosis, nausea, and vomiting). In the presence of fever, larger amounts are commonly necessary. Each child is a law unto himself and the parents soon learn how much to administer and how often. It is rare indeed that more than 0.5 cc. ($7\frac{1}{2}$ minims) is required, although I once saw a child of two years who required 1.0 cc. (15 minims) for relief. I have a rough but highly practical rule to the effect that any child who has to have an injection of epinephrine as often as every four hours should be hospitalized.

Occasionally an individual is encountered who cannot tolerate epinephrine because of tremor, palpitation, nervousness or other disagreeable reactions. In such cases ethylnorepinephrine* may prove

* Marketed by Winthrop Stearns as Butanefrine and by G. A. Breon & Co. as Bronkephrine.

very useful, especially in children. This is a sympathomimetic amine which may prove very useful, especially in children. This does not raise the blood pressure and ordinarily has very little stimulating effect on the central nervous system. It is supplied as the hydrochloride salt in a one to five hundred dilution and the dose is commonly twice that of epinephrine one to one thousand.

Occasionally epinephrine in oil, 1:500, because of its slow absorptive properties and prolonged action, is of great value in individual cases. It is more painful than the aqueous solution and may leave somewhat tender lumps which are slow in disappearing. The dose is commonly twice that of the aqueous preparation. Since the epinephrine is a suspension in oil, care must be taken to use a perfectly dry syringe, otherwise the water in the syringe will dissolve out the epinephrine suspension and overdosage may occur. It is important to be sure that the child is not sensitive to the oil used to suspend the epinephrine (peanut oil in the Parke, Davis and Company and Squibb preparations, and sesame oil with Winthrop Stearns). A gelatin preparation by Smith is also available.

Ratner (21) reported a four-year-old boy who was given 1.0 cc. of adrenalin in oil (Parke, Davis) into the buttocks by his family physician. The area of injection remained indurated and gradually, over a period of three months, spread and fluctuant areas appeared. The swelling was dull red in character and about 7 cm. in diameter. The surgical consultant diagnosed an oleoma which he incised and shelled out. The boy was not clinically sensitive to peanuts.

More recently, instead of epinephrine in oil, we have been using Sus-Phrine.† This was devised by Naterman (17) and favorably reported upon by Unger and Unger (22). It consists of a 1/200 suspension of epinephrine in a base of 10 per cent glycerine, 2 per cent sodium thioglycolate, and 0.5 per cent chlorbutanol. This is much simpler to administer than epinephrine in oil as it is an aqueous solution and can be administered through an ordinary hypodermic needle in the same manner as the usual aqueous epinephrine. Relief of asthma, when it is effective, is experienced in ten to twenty minutes and lasts on the average, six to ten hours or more. We find the average dose for children to be 0.10 cc. to 0.15 cc. according to the severity of the attack.

If the infant or child is unduly restless or apprehensive, I occasion-

† Manufactured by Brewer and Company, Inc., Worcester, Mass.

ally give a small amount of Demerol (Winthrop-Stearns) solution mixed in the same syringe as the epinephrine. This is not, however, a routine measure. The dose is calculated according to body weight (average adult dose 100 mg.) and only half to one quarter of the calculated dose is employed. This is because the exhausted respiratory center may be very susceptible to even small doses of narcotics and for this reason standing orders for the administration of these drugs should never be written. The absorption of the Demerol is greatly prolonged by its mixture with the epinephrine. In such doses, the drug apparently exerts its antispasmodic and sedative effects without the respiratory depression commonly caused by opium derivatives.

The burning of "asthma powders" may occasionally relieve a child or infant when other commonly used measures have failed. The active ingredients of these preparations is stramonium powder (2 parts) mixed with an oxidizing agent, potassium nitrate (1 part), and a fuel, such as powdered anise (1 part) (11). The use of this mixture is not recommended as a routine method of treatment as the smoke is irritating and the odor disagreeable. However, some parents who have difficulty in the administration of other medications to their child do occasionally appear to obtain satisfactory relief by this method.

At the time of the first visit of an asthmatic child, we commonly give the parents a reprint, "Care of the Child with Chronic Asthma," (10) and ask them to study this carefully and do their best to make a personal application.

Therapy with ACTH and cortisone is not ordinarily employed for the treatment of asthmatic attacks which can be controlled otherwise. These drugs in the treatment of asthma will be discussed subsequently (see Chapter 37).

At this point, it might be worth while to mention that there is no evidence whatever that vitamins are specifically of value in the treatment of bronchial asthma. Dilantin sodium, ethylene disulphonate, hapamine, histamine, histaminase, potassium chloride and sulfur in

The specific treatment of bronchial asthma in infants and children by the injection of extracts of allergens differs in no essential particular from that of adults. It is considered fully in the standard textbooks (see Table XXXIX) which should be consulted for details. Environmental control and diet for children, on the other hand, are fully described in this volume and the symptomatic treatment of bronchial asthma in infants and children, discussed in this and other chapters.

oil have all been without value in the treatment of bronchial asthma in my experience.

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STATUS ASTHMATICUS

IF THE PATIENT cannot be relieved by the injection of epinephrine, he is then said to be “epinephrine fast” and in “status asthmaticus.” While this happens less commonly with children than with adults, it may happen at any age, even under one year.

The most important error made in the treatment of status asthmaticus is *failure to keep the patient well hydrated*. This results in plugging of the smaller, and sometimes the larger, subdivisions of the bronchi with thick, inspissated plugs of mucus which the patient cannot cough up so that death eventually may result by suffocation. The bronchial secretions are best kept thin by plenty of fluid administered parenterally. Table XII (17) indicates the fluid require-

TABLE XII
RANGE OF AVERAGE WATER REQUIREMENTS OF CHILDREN AT DIFFERENT
AGES UNDER ORDINARY CONDITIONS (17)

Age	Average Body Weight kg.	Total Water in 24 hours cc.	Water Per kg. Body Wt. in 24 hr. cc.
3 months	5.4	750- 850	140-160
6 months	7.3	950-1100	130-155
9 months	8.6	1100-1250	125-145
1 year	9.5	1150-1300	120-135
2 years	11.8	1350-1500	115-125
4 years	16.2	1600-1800	100-110
6 years	20.0	1800-2000	90-100
10 years	28.7	2000-2500	70- 85
14 years	45.0	2200-2700	50- 60
18 years	54.0	2200-2700	40- 50

ments of children. Other measures for keeping the secretions thin are by the use of expectorants, and steam (preferably cold, if the patient is in an oxygen tent) or by otherwise dampened air.

Because these patients have had repeated injections of epinephrine and have usually been taking little or no nourishment, their glycogen

reserves are markedly depleted. Therefore much of the parenterally administered fluid should contain dextrose. My present practice with a child in status asthmaticus, if he is at all dehydrated, and most of them are, is to start immediately an intravenous drip of 5 per cent dextrose in distilled water, 500 to 1000 cc., to which is added 0.25 or 0.50 gm. of sodium iodide (for its expectorant effect). After the drip has been started the proper dose of aminophylline is given through the intravenous tube. If desired, at least twice that dose may be given by the drip mixed with the dextrose and sodium iodide.

At the time of insertion of the drip, blood is obtained for a potassium level and as soon as possible thereafter an electrocardiogram is made. This is for the purpose of comparing with future electrocardiograms for controlling potassium balance in case ACTH or cortisone is used later. These drugs are indicated if the above measures fail to bring the patient out of the asthmatic attack. If the child becomes nauseated, the aminophylline and sodium iodide are best omitted from the drip which is continued with a 5 per cent dextrose solution.

AMINOPHYLLINE

Aminophylline is often highly effective and is usually well-tolerated in the symptomatic treatment of bronchial asthma. The lethal dose for man has never been determined but is doubtless far beyond the therapeutic range. At one time on attempting to investigate this problem I was told by the research directors of several large manufacturing firms that they had reports of truly fantastic amounts having been injected intravenously by error without serious results. The deaths thus far reported as having followed the intravenous injection of aminophylline have all occurred in adults with heart disease; no deaths from aminophylline have been reported in children.

It would be a grave mistake, however, to assume that aminophylline in pediatric practice is an entirely harmless drug. Lee (8) stated that she had seen several sterile abscesses following the supposedly intramuscular injection of aminophylline and that, when given too rapidly or in too large amounts, intravenously administered aminophylline has produced profound shock necessitating intravenous fluids and cardiorespiratory stimulation. Berkowitz and associates (2) noted that "side reactions" to aminophylline, which

they regard as in all probability minor allergic reactions, occurred in 11.5 per cent of eighty asthmatic children.

A most valuable contribution to this subject has been made by Rounds (12) who observed six cases of aminophylline toxicity in children varying in age from eleven months to three years over a three-year period. Rounds pointed out that the toxic actions of aminophylline are those of xanthine derivatives which include caffeine, theobromin, and theophylline. Aminophylline is theophylline combined with ethylene diamine. These reactions manifest themselves in three categories: (1) extensive stimulation of the central nervous system; (2) gastric irritation associated with severe vomiting, and (3) effects upon the kidneys as evidenced principally by albuminuria. In the cases reported by Rounds, the chief symptoms of aminophylline intoxication, which were attributed to overdosage in most instances although specific sensitivity to the drug could not be ruled out, were severe vomiting, sometimes bloody, with resulting dehydration. This occurred whether the aminophylline was given in the form of rectal suppositories, intravenously, or, in one case, intramuscularly. Convulsions and other neurological evidences of cerebral edema were observed in some instances. Albuminuria was occasionally present but might have been due to other causes than the direct action of the drug upon the kidneys because all these children were critically ill. It is quite significant, however, that in one case, despite the severe reactions apparently due to the aminophylline and the critical illness of the children due to this and to the primary disease, death occurred in only one instance and this was not attributed to the aminophylline.

It is evident, as Rounds has stated, that considerable caution should be exercised as regards the dosage of aminophylline. If combined, as suppositories often are, with some other drug, particularly a barbiturate, sensitivity to this drug must also be considered in addition to the possibilities that reactions may occur to the excipients of which the suppository is composed or because of sensitivity to the aminophylline itself. The smallest aminophylline suppository commercially available is the so-called "child size" or 0.25 gm. This may be split lengthwise or in quarters for administration of smaller doses. The wide range of absorbability of aminophylline rectally in different individuals, as has been pointed out by Waxler and Shack (16), is

also a factor in the variety of effects produced by this drug.

For therapeutic purposes in bronchial asthma, the dose of aminophylline for infants and children is in the same proportion to the body weight as for adults; 0.003 to 0.006 gm. per kg. (0.025 to 0.05 grains per lb.) as a single dose, assuming that 0.25 to 0.50 gm. ($3\frac{1}{4}$ to $7\frac{1}{2}$ grains) is the correct dose to be given to a 75 kg. (150 lb.) adult intravenously or rectally. Aminophylline alone is rarely administered orally to infants and children because of their inability to swallow tablets intact, its bitter taste and tendency to cause severe gastric irritation in adequate therapeutic doses. There is also evidence, as Segal (14) has shown, that aminophylline, which works well intravenously or rectally, is relatively ineffective when given either intramuscularly or by mouth.

Any leakage of aminophylline around a vein into the subcutaneous tissues is very painful and when this occurs a local anesthetic, such as 1 per cent procaine should be injected. Aminophylline is also supplied in 2 cc. ampoules containing 0.5 gm. ($7\frac{1}{2}$ grains) for intramuscular injection. This, however, is very painful and should be preceded by the administration of a local anesthetic.

OTHER MEDICATIONS IN STATUS ASTHMATICUS

Brown (3) has advocated the intravenous injection of ethyl alcohol and this has been employed in children by Bacal and Pedvis (1) who consider it of value. The suggested dose is 2 cc. per kg. of body weight (about 1 cc. per lb.) of 95 per cent alcohol administered in a 5 per cent dextrose solution (or 40 cc. per kg. of 5 per cent alcohol in saline or dextrose solution). The alcohol not only supplies calories, but acts as a sedative, particularly useful in allaying apprehension.

As soon as possible the child should be started on expectorants by mouth. By far the best is potassium iodide. A child of three years may be given 5 drops of a saturated aqueous solution, preferably after meals and well-diluted with water or milk. On rare occasions this may disagree, causing a rash, gastric distress or other symptoms. Possibly the next best expectorant is glyceryl guaiacolate.*

* A convenient preparation of this is Robitussin (Robins) which contains 100 mg. of this drug with 1 mg. of desoxyephedrine hydrochloride in one teaspoon. Toclase (Pfizer) which contains carbetapentane citrate 7.25 mg. and menthol 0.5 mg. in a 5% alcoholic syrup is also very helpful. The dose for children is one teaspoon (5 cc.) three or four times a day.

In status asthmaticus, because the lungs are edematous and particularly subject to infection, an antibiotic, as penicillin, should be administered in a large initial dose, e.g., 600,000 units and continued until the child is well out of the attack. If the child actually appears to have an infection streptomycin should be given as well, at least until the reports of the throat and sputum cultures are obtained.

Demerol (Winthrop-Stearns) is occasionally employed in status asthmaticus for the same reasons and in the same dosage with the same precautions as in the treatment of the acute attack (see Chap. 36). Only a minimal amount of epinephrine 1/1000 is, however, given with the Demerol, usually 0.10 to 0.20 cc., depending upon the size of the child, as the epinephrine in status asthmaticus has no effect upon the asthma and is given only to slow down and prolong the action of the demerol.

ACTH AND CORTISONE IN STATUS ASTHMATICUS*

The indications as to which of these drugs should be used first are not yet clearly established. It would seem reasonable to start with cortisone because the adrenals may be assumed to be exhausted by the stress imposed by the asthma, and the condition of the patient does not permit loss of time by the performance of eosinophil response tests. If it is possible to take the cortisone by mouth, it is preferably administered in that manner, and the child is given 50 to 75 mg. every eight hours until he begins to respond; then the same dose is given every twelve hours, and after another twelve hours is gradually reduced by 25 mg. or less every eight hours to the amount which will keep the asthma under control. If the child is unable to take oral medication, the same doses are given by intramuscular injection. In general, the dose depends upon the severity of the attack and not altogether on the age or weight of the infant. Failure to respond generally indicates too small a dose. In the case of two infants with severe status asthmaticus under one year of age, and who were critically ill, in each instance a starting dose of 100 mg. was given intramuscularly and continued with 50 mg. every six hours. The infants came out of the attack very nicely, ap-

* In conjunction with this section the reader is advised to study the general discussion of ACTH and cortisone in Chapter 39.

peared to have suffered no ill results of any kind, and eighteen hours after the initial dose the blood potassium levels and electrocardiograms were normal. The usual interval required for response to therapy by ACTH or cortisone is six to eighteen hours, with an average of about eight hours.

If cortisone is not available or is too expensive for the patient, or is otherwise contraindicated, ACTH (aqueous only) should be given intravenously. It is commonly highly effective when given by this method, and only small amounts are required. This was first demonstrated by Gordon (5), and reported in further detail by Renold and associates (11) and by Mandel and associates (9). The usual dose for adults is 20 units in 500 cc. of normal saline or 5 per cent dextrose. I prefer the dextrose solution in order to avoid giving added sodium. For infants and children the dose is commonly 10 units of ACTH in 500 cc. of 5 per cent dextrose given by a very slow intravenous drip over an eight-hour period. It is interesting that larger doses do not appear to increase the response, and if the same dose is given rapidly intravenously there is practically no beneficial effect of any kind. Aminophylline should not be given in the same solution as the ACTH because its alkalinity probably has a deleterious effect on the ACTH. However, potassium chloride 0.2 per cent may be administered with the dextrose and ACTH in order to counterbalance the potassium diuresis caused by the ACTH.* Potassium should not be administered unless the patient is voiding well.

Mandel and associates (9) report that undesirable reactions made cessation of intravenous ACTH necessary in seven adults. The common complaints were during the first few hours of infusion and consisted of flushing of the face, or a feeling of tightness across the chest, or a sense of fullness in the abdomen. The longest period of continuous treatment for any one patient was forty-two days. In a fairly limited experience with children we have experienced no serious reactions and it was not necessary to continue the treatments for more than three or four days.

Hydrocortisone for intravenous use is now available, but at the time of this writing it cannot be decided whether it has any marked

* Kaladax of the Baxter laboratories, which consists of 0.2 per cent potassium chloride in 5 per cent dextrose in distilled water, is very convenient for this purpose.

advantage over ACTH in the emergency treatment of severe allergies.

INTRAMUSCULAR ADMINISTRATION OF ACTH

If it is elected to administer ACTH by intramuscular injection, the dose is commonly 10 to 20 units of the aqueous preparation every six hours, or twice that of the slowly absorbable preparation every twelve hours, until the asthma is under control, usually a matter of six to eighteen hours. Smaller doses are not commonly effective, even under one year of age. When the asthma is under control, the dose is gradually decreased and the interval between injections is increased to the minimum required to keep the patient under control.

Mandel and associates (9) further state that ACTH may be given by intramuscular drip. When this is done, 10 cc. of 1 per cent procaine is added for each liter of the drip and 300 TR units of hyaluronidase deposited at the site of the injection. The solution is dripped into the muscles very slowly corresponding to the intravenous drip. Renold and associates (11) state that the intravenous administration of ACTH resulted in a normal response in four adults who had become unresponsive to the same preparation of ACTH injected intramuscularly. That a tissue factor is responsible for the destruction of the ACTH under such circumstances is further suggested by the fact that the intramuscular injection of a similar dose of ACTH as a constant drip comparable in time to that given intravenously failed to result in any fall of the eosinophils in one such unresponsive patient.

We have, thus far, had no disagreeable experiences as a result of administering cortisone or ACTH in status asthmaticus. However, it is quite possible that, with more extensive experience, some difficulties may be encountered. These will perhaps be associated with the potassium deficiency which may be induced by these drugs because they cause the excretion of potassium into the urine. The difficulties which may arise as the result of too little potassium in the blood (hypokalemia), or too much (hyperkalemia) as a result of attempting to compensate for this, will be discussed subsequently, as will also the problem of maintenance therapy in chronic, intractable asthma.

OXYGEN IN STATUS ASTHMATICUS

Oxygen should be administered in severe or prolonged asthmatic attacks without waiting for the child to show clinical evidence of cyanosis. Cyanosis does not occur commonly unless the child is critically ill. Holinger and associates (7) have studied the actions of gas inhalations in bronchial asthma with very interesting results. They report that gas inhalations are quite specific and grossly influence the physical and chemical qualities of both the expectorated and the bronchoscopically obtainable sputum, as well as the character of the bronchial mucosa. Steam inhalations of a high humidity atmosphere result in the liquifaction of sputum. Carbon dioxide has a reaction quite similar to that of steam, but to a greater degree, and, in addition, it increases the resorbing power of the bronchial mucosa; consequently, it may be considered an extremely efficient expectorant. Oxygen, on the contrary, acts very specifically as an antiexpectorant, and, therefore, if used alone is contraindicated in obstructive lesions which are, in part at least, due to copious viscid secretions. This deleterious effect may be neutralized partly or wholly through the addition of steam and 5 to 10 per cent carbon dioxide.

I have had no experience with the use of helium and oxygen in children and have not been impressed by what I have seen of its use in adults.

BRONCHOSCOPY IN STATUS ASTHMATICUS

As yet, I have not had under my care a child in uncomplicated status asthmaticus who has not responded to the procedures previously discussed. Others have, and in such cases bronchoscopy is recommended for the purpose of aspirating the thickened secretions. The youngest patient treated by Holinger* was two years of age. It is evident, however, that if bronchoscopy is to be done, it should be carried out fairly early and not as a terminal procedure which would precipitate the exitus.

MISCELLANEOUS PROCEDURES IN STATUS ASTHMATICUS

Ether and olive oil in equal parts, administered rectally, 3 cc. per kg. (1 oz. per 20 lb. body weight), is recommended for adults.

* Personal communication to the author.

but I have had no experience with this for children. The same is true of the use of avertin (tribromethanol) administered rectally, although an occasional older individual has responded satisfactorily.

I saw in consultation at one time, before the advent of steroid therapy, three adult asthmatics, all of whom were epinephrine fast and had not been relieved by the intravenous administration of aminophylline or any other measures. They were all critically ill. All three responded to the administration of procaine hydrochloride by intravenous drip. The method used was that described by Schrum (13) for use in other conditions. The dose was 4 mg. per kg. body weight of patient in an 0.1 per cent solution in normal saline or 5 per cent dextrose. In at least two of these cases, the use of this procedure appeared life saving. I have subsequently tried it in other adults without beneficial results. I have not used this since the advent of ACTH and cortisone. The use of procaine intravenously is not without danger, although I have not seen any reports of severe idiosyncrasy to this drug in infants and children.

In closing this discussion on the treatment of status asthmaticus, one final point should be made. The patient with status asthmaticus should not routinely be given drugs which do not relieve his condition, but which may further aggravate it by making him nervous or drying his secretions. This very often happens in hospital practice where the drugs most commonly at fault, ephedrine and one of the antihistaminics, are often prescribed as routine measures.

EPINEPHRINE POISONING

Since epinephrine is one of the most common and important drugs used in the treatment of bronchial asthma, it would seem proper to discuss here the treatment of accidental overdosage of this drug, since this occasionally occurs and may be very serious. The treatment of epinephrine overdosage has been described by Möller whose paper was abstracted into English by Hanzlik (6) and also by Glaser (4). Möller recommended giving inhalations of amyl nitrite (3 drops) vapor as quickly as possible followed by a larger dose (2.0 to 4.0 mg.) of nitroglycerin by mouth and then erythrol tetranitrate in divided doses of 5 mg. to a total of 20 mg. intravenously to control the high blood pressure and promote recovery according to individual requirements. Möller had employed these measures suc-

cessfully in the case of a twelve-year-old girl who had through error received a subcutaneous dose of epinephrine equivalent of 20 cc. of the usual 1/1000 solution which is double the known fatal dose for an adult man.

Möller also mentioned that the site of injection of the epinephrine may be excised. I should, however, like to suggest an immediate alternate emergency measure in the case of injections into an extremity. It is the placing of a tourniquet proximal to the site of the injection and releasing this at intervals, just as is done in preventing severe pollen reactions when an overdose is inadvertently administered.

I should also like to suggest that an ideal method of treatment might be the immediate intravenous or intramuscular injection of one of the drugs used in the diagnosis of pheochromocytoma, particularly Regitine (Ciba) which is 2(m-hydroxy-N-p-toly lanilin-methy)-2-imidazoline, a relative of Priscoline. This drug blocks the pressor effect of circulating epinephrine and nor-epinephrine though the latter is twice as resistant to this inhibitory effect. Regitine is suggested because, according to Soffer's (15) review, it is the best pharmacological test for sustained hypertension or for use at the height of a paroxysm of hypertension. Probably, in the treatment of epinephrine overdosage, the same dose as suggested as a diagnostic test in pheochromocytoma should be used. For children, this is 1 mg. intravenously or 3 mg. intramuscularly, and repeated as indicated. The drug is supplied in ampoules, each of which contains 5 mg. of Regitine in lyophilized form to which 1 cc. of distilled water is to be added in preparation for use.

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CHAPTER 38

MANAGEMENT OF THE CHILD WITH CHRONIC ASTHMA

WHILE asthma, in general, is a chronic, recurring disease, for purposes of this discussion the child with chronic asthma may be considered as a child who has persistent perennial attacks, even though they may be symptomatically well controlled by one method or another. For purposes of this discussion, the treatment of such a child may be considered under a number of headings, of which the most important are prophylaxis, environmental control, climate, protection against infection, education, physiotherapy, and psychosomatics. The subjects of psychosomatics, climate, and prophylaxis as related to the allergic child will be discussed elsewhere in this book (see Chapters 59, 64, 66, 67). The remaining facets of this problem will be discussed at this time.

ENVIRONMENTAL CONTROL

The parents of such a child must be prepared to accept the fact that, as in any other chronic disease, as diabetes, for example, the whole design of family life must revolve around the afflicted child. This may not be easy. The mother, whose heart is set on loading her home with overstuffed furniture and draperies and other types of furnishings particularly likely to produce or to hold dust, and the father, whose hunting dogs are his pride and joy, must adjust themselves to the sacrifices made necessary as a result of the illness of the child.

The home must be kept as free from dust as possible. Particular attention must be paid to the child's room. Detailed directions for accomplishing this may be obtained from any manufacturer of dust-proofing fabrics or from any allergist (See Table XXXI, Addenda).

Complete air conditioning of the houses of the future, although designed primarily for comfort by affording an even temperature with a satisfactory moisture content and to make the work of the

housewife easier by eliminating dust, will eventually be of inestimable value in the care of these patients. The preferred form of heat is hot water or steam, because heating by hot air ducts is a very effective way of stirring up dust currents. The new form of convection heating by means of pipes coiled in the floors, walls or ceilings through which heated fluid is circulated should prove ideal. The bedding in the child's room should be free from feathers and wool regardless of skin tests and also free from other allergens as may be indicated by the history and skin tests. There should be no feather pillows in the child's bedroom and preferably none in the house. The pillows should be of sponge rubber and covered with dustproof covers to prevent dust from settling into the pores of the rubber. The mattresses also should preferably be made of sponge rubber and, in any event, should be covered with dustproof material. The blankets should be made of glass wool or some other synthetic fiber.* There is now a wide choice of synthetic fibers for snow suits and other clothing as a substitute for wool. Unfortunately, glass fiber has not proven satisfactory for making pillows or the insulation of clothing.

The child should sleep in a room which is not uncomfortably cool certainly not below 68°. He should never get out of bed onto a cold floor in his bare feet or walk about barefooted. It is necessary that the asthmatic child be adequately protected from the weather, even though in accomplishing this one is forced to run counter to the fashions of the times. It is important to wear a head covering unless the weather is really warm. In wet weather the feet must be properly protected by rubbers which are also useful as protection from cold pavements. In cold weather bare legs and knees are an invitation to trouble, a fact which is often difficult to impress on the mind of the child of high school age.

Strong odors are to be avoided by the child with chronic asthma. The odor of fresh paint is a particular offender and no painting should be done while the child is in the house nor should the child

* Peerless (Dynel) blankets made of vinyl fiber are manufactured by Pepperell, 40 Worth Street, New York 13, N.Y. Quilted celanese Jersey blankets (Hego's Intereel) are manufactured by Jack Turk and Company, 132 West 36 Street, New York 18, N.Y. Doubtless many other plastics will also be found suitable for the making of bedding.

return until the odor of the paint has completely disappeared. The odor of burning leaves is also particularly to be guarded against. One of the most glaring of our present day social defects is the utter disregard which most smokers show for the feelings of others regarding tobacco smoke, an important and nearly always a nonspecific irritant in bronchial asthma. The family must also guard against the use of strongly scented perfumes and other toiletries. The odors of flowers, gasoline, kerosene, moth balls, and cleaning fluids must also be avoided. Occasionally a child exquisitely sensitive to a food may react with asthma to the odor of the food, as has been discussed by Horesh.* Such foods are best kept out of the house, and at least in such cases the kitchen should be provided with a ventilator to remove the odors of these foods and also such other cooking odors as may be irritant even though nonspecific.

One of the most difficult problems in environmental control is that of family pets. It may be stated categorically that there should be no animal pets with fur or feathers in the household of an allergic individual, regardless of the results of skin tests. Sensitivity to epidermoids is so easily acquired that the presence of such animals is an invitation to trouble. I have several times had the experience of seeing a child with chronic asthma clear completely following the removal or death of the family pet which had been retained against advice, usually because the child gave a negative skin test or showed no evidence of asthma on contact with the animal so that the parents felt that they might reasonably take the gamble of keeping the pet. The futility of relying on skin tests is indicated by the work of Hooker (6) which showed that different breeds of dogs may give specific skin tests for the breed but not for dogs as a whole, so that, to be of significance, a child should be tested with an extract of the dander of his own pet. What holds true for dogs presumably holds true for other animals as cats, chickens, etc., though probably to a lesser extent.

EDUCATION

The training of the child for eventual self-support must be considered in the case of the child with chronic asthma. But one study has been made of this subject. Flensburg (3), in Denmark, investi-

* For bibliography see Chapter 60.

gated 298 asthmatic children and stated that 116 of these or about one-third had chosen a special profession on account of their asthma. It must always be borne in mind that once an individual suffers from asthma, even though a complete recovery may have been made, just as in the case of tuberculosis, there is always the possibility that a relapse may occur. This was well illustrated during the last war when many of my former child patients who had been discharged as "cured" again developed asthma when exposed to the rigors of military life.

There are certain occupations which are obviously unsuited for the asthmatic individual. These involve heavy manual labor and other forms of excessive physical activity as professional athletics or the teaching of physical education; exposure to excessive dust, cold, moisture, strong odors, high or low temperatures and sudden changes in temperature. Bakers may develop asthma from exposure to flour dust; farmers, as well as veterinarians and others exposed to animals, are often sensitized to various epidermoids; beauty parlor operators are often sensitized to ingredients of cosmetics. It seems reasonable that asthmatic children should not, if they take up music, study wind instruments. The use of such instruments is difficult for dyspneic individuals and it is also probable that they increase the tendency to emphysema present in all asthmatics. It is of the utmost importance that the asthmatic child should be aided in the selection of a career in which, if asthma persists or recurs, the earning of a living will not be impossible.

PHYSIOTHERAPY IN BRONCHIAL ASTHMA

The most common complication of long continued bronchial asthma is emphysema. In the adult this results in the typical picture of the "barrel shaped" chest with the shoulders elevated, the back hunched and the head thrust forward. Long continued bronchial asthma in the child produces a different type of deformity described in detail by Bock (1) and which, because of its resemblance in some respects to rickets he has termed "pseudorachitis asthmatica" or "asthmatic pseudorickets." This has been discussed on page 221.

Weiser (8, 9) of Palestine has reported particularly brilliant results in the treatment of asthmatic children by physiotherapy. He states that the exercises employed are indicated in all cases of

bronchial asthma showing a low vital capacity and cramped superficial breathing with poor chest expansion and little use of the diaphragm. Fisher (4), in England, also reports good results from the use of exercises with less satisfactory progress in the "lung damage" type of asthma. Physiotherapy in this direction has been explored very little in this country and should be a fertile and productive field for investigation.*

CONCLUSION

A very common error made in the treatment of the child with chronic asthma is failure to continue treatment after the child has been doing well for a period of weeks or months. Treatments should not be stopped until the child has been completely free from symptoms for a period of at least one year. If the child has been receiving injection treatments and is doing well, the intervals between the treatments may commonly be increased by increments of one week until the injections are given every four weeks, but the child should be symptom free for at least one year before the treatments are discontinued.

Finally, it must be stated that there is a fairly large group of children, as well as adults, who suffer severely from and are more or less totally incapacitated by bronchial asthma who cannot be satisfactorily relieved by the measures outlined in the foregoing discussion. These patients demand care and study beyond that which their physicians can give, even with the best hospital facilities. There are now in this country few institutions where an asthmatic cripple may go for care and study, regardless of ability to pay. The oldest and best known of these is the Jewish National Home for Asthmatic Children in Denver (5).† The need for an organization to develop and support similar institutions available for everyone and to do for asthmatics what the National Foundation for Infantile Paralysis, for example, is doing for individuals with poliomyelitis, is acute. This has been realized for many years. It is hoped that the Founda-

* A very splendid little booklet, "Physical Exercises for Asthma," published by the Asthma Research Council, will be found most helpful for home use by the patient interested in this form of therapy. It may be obtained at nominal cost by writing the Secretary of the Council, King's College, Strand, W.C. 2 London, England.

† See also Chapter 64.

tion for the Allergic Diseases of the American Academy of Allergy and the American College of Allergists will eventually serve this purpose.

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THE TREATMENT OF ALLERGIC DISEASES WITH CORTICOTROPIN (ACTH) AND CORTISONE

IT IS NOT the purpose of this volume to review in detail the fascinating history of the development of these drugs, but a short summary would appear to be in order. This was admirably done by Scheie and associates (11) and the following is taken largely from their publication. In 1924, Evans first reported that pituitary extract prevented the atrophy of the adrenal gland which results from removal of the pituitary body in animals. Collip, in 1933, first isolated the fraction which prevented this atrophy, the adrenocorticotrophic hormone, or ACTH. Koch, Hays and others (1) later purified this preparation in the Armour laboratories. Thorn and his associates (12), in 1946, first injected ACTH into man and demonstrated that it stimulated the adrenal cortex. Mason, Myers, and Kendall (5) in this country, simultaneously with Swiss investigators, Reichstein, Wintersteiner and Pfiffner, identified cortisone (17-hydroxy-11-dehydrocorticosterone), or Kendall's compound E, which is secreted by the adrenal cortex. It was first synthesized in 1946 by Sarrett (10) and made available for clinical use through the cooperation of Merck and Company and Kendall and his associates at the Mayo Clinic.

The present concept is that the secretion of cortical steroid hormones is mainly or entirely mediated through stimulation of the adrenal cortex by the adrenocorticotrophic hormone (ACTH) of the anterior pituitary gland. The hypothalamus is believed to exert some degree of control on anterior pituitary function, either directly through nerve fibers or indirectly through a humoral mechanism. Hypothalamic activity may, in turn, be influenced by higher brain centers. ACTH reaches the adrenals through the blood. Epinephrine, elaborated by the adrenal medulla, may also stimulate the anterior pituitary to release ACTH.

When the adrenal gland is stimulated, three general types of cortical hormones or corticoids are secreted:

1. Compound F-like hormones (17-hydroxycorticosterone-like steroids).

2. Desoxycorticosterone-like hormones.

3. Adrenal androgens.

These hormones, very briefly and incompletely stated, have the following principal actions:

1. *Compound F-like Hormones* (17-hydroxycorticosterone-like steroids). These are the principal hormones secreted by the adrenal gland. They cause *glycogenesis* to restore the glycogen stores that are used up in the "alarm reaction" or reaction to acute "stress" situations. They may also mobilize fat from the fat deposits as a source of energy and possibly for conversion to glucose and glycogen. Overstimulation will result in hyperglycemia and glycosuria. *This is not true diabetes.*

These hormones also *mobilize amino acids from the tissue proteins* for the purposes of providing energy, for conversion to glucose and glycogen, and for making amino acids available for protein synthesis in wounded or abnormal tissue. This causes increased excretion of nitrogen, phosphate, calcium and *potassium*.

2. *Desoxycorticosterone-like Hormones*. These cause retention of sodium and chloride with concurrent retention of fluids and decreased sweating, and *increased secretion of potassium*. With maximum stimulation there may occur edema and *potassium deficiency*.

3. *Adrenal Androgens*. These are androgenic and anabolic in character. This may represent a balancing mechanism against the protein catabolic effect of the Compound F-like hormones. When administered in excess, particularly to females, they may cause masculinization, hirsutism, and amenorrhea.

INDICATIONS FOR HORMONE THERAPY

In the present light of our knowledge, generally speaking, these hormones, which are in no way curative, should be reserved for those allergic diseases which have resisted all efforts for relief by the orthodox methods and not used as primary medications. We do not yet know what the long-term effects of these drugs will be after the lapse of several years and we do know that they are powerful

medicines which produce profound metabolic changes. The only exception to this rule is perhaps in the case of severe acute attacks of allergic disease, such as severe contact dermatitis, drug reactions, anaphylactic reactions of various types, stings and bites by poisonous insects or reptiles. In general, in these conditions only short, intensive courses of therapy are required and because of their great efficiency, often life saving, it does not seem logical that these drugs should be withheld.

GENERAL PROCEDURES

When we first started the use of these drugs, our patients were all subjected to very rigorous laboratory investigation, which included hospitalization, Thorn tests (13), complete blood counts and urine examination, weight and blood pressure every other day, total blood proteins, albumin-globulin ratio, serum chlorides, sodium, potassium, glucose, and CO_2 combining power. An electrocardiogram was made and glucose tolerance tests and urea clearance tests were also commonly done.

At the present time, we do not do all these tests nor do we feel it commonly necessary to hospitalize the patient, although we prefer to do this as it enables us to test the effect of a change of environment. The procedures commonly done are now as follows, it being understood that at this point the child has had a complete pediatric and allergic study and has not had satisfactory relief from his disability:

1. Weight.
2. Blood pressure.
3. Urine examination—usual routine.

While under treatment, items 1, 2, and 3 are checked every week for a month and then at two-week intervals for another month and then three or four-week intervals. Other tests than those mentioned above are done as indicated. For short-term therapy, such as, for example, the treatment of poison ivy, we do not regard it as essential to perform any of the above tests.

CHOICE OF DRUG TO BE USED

It is my feeling that for long-term therapy ACTH is the drug of choice in infants and children because it offers a more nearly physio-

logic approach. This causes hypertrophy of that part of the adrenal cortex producing Compound F (17-hydroxycorticosterone) which has essentially the same effects upon the body as cortisone (11-dehydro-17-hydroxycorticosterone) or Compound E of Kendall. I feel that it is possible, in the case of children at least, with their strong tendencies toward spontaneous recovery, that this may be favored by ACTH which causes hypertrophy of the adrenal cortex which may possibly persist somewhat, whereas cortisone therapy, which is substitution therapy, causes atrophy of the adrenal cortex, which is, however, reversible when the drug is discontinued.

We have used cortisone in those cases (1) where the parents or other available members of the family could not be taught or depended upon to give the injections of ACTH, (2) where the child, by virtue of dominating the home, rendered hypodermic injections impractical or impossible, (3) where only short-term therapy was to be tried, for instance, in clearing the skin for direct testing, and (4) where the child did not respond to ACTH in adequate dosage. This occurred in only one instance.

Dosage as regards atopic dermatitis and asthma has been previously discussed (see Chapters 19 and 37), and will be further discussed for other allergic diseases as they are considered.

While on ACTH or cortisone we do not limit the diet but advise that only a minimum of salt (sodium chloride) be used in the preparation of the food and that no additional salt be added on serving. We do not use potassium chloride because this quite often results in gastric irritation, but prefer instead the mixture recommended by Randall and associates (9). The prescription for its preparation is as follows:

Potassium acetate			
Potassium bicarbonate			
Potassium citrate	aa	15.0	Oz. ½
Aqua qs ad		120.0	Oz. iv

Each teaspoon of this preparation contains about 13 mEq. of potassium. The dose for an adult (children in proportion to size) is one teaspoon three or four times a day well diluted in a flavored beverage. Potassium iodide is not satisfactory as a source of potassium since the usual adult dose of 10 drops of the saturated solution supplies only 3 mEq. The use of citrus fruit juices is encouraged

because of their relatively high potassium content. The contraindications to potassium administration will be discussed subsequently, but it is well to re-emphasize here that this drug should not be given with impaired renal function or in severe dehydration.

When a patient is first started on ambulatory treatment with steroids, the mother is requested to report daily by telephone during the first week, and at least once a week thereafter if the child is unable to come into the office for a weekly check-up. Since it is well known that ACTH and cortisone may mask acute intercurrent infections, while on these drugs the patients must be carefully watched for any slight abnormality which might indicate infection and vigorously treated should such evidence appear. In the case of children with frequent recurrent respiratory infections it is well to keep them on running doses of penicillin or a sulfon drug or both (see Chapter 67).

If the same child has both atopic dermatitis and asthma, generally speaking, larger doses appear to be necessary to control the asthma than the eczema. We have had the opportunity of observing this only in a limited number of cases, however, and it is quite possible that, with further experience, it may be necessary to modify this statement.

We have carried along several asthmatic children for at least two years on ACTH injected by the mother at home or on oral cortisone. Occasionally, these children have done well on doses as low as 5 units of ACTH every four days. Usually, when we reach a dose that small, the ACTH is discontinued after a month of freedom from asthma, and in some instances there has been no recurrence; in other instances the recurrences have been mild and infrequent and easily controlled by symptomatic treatment. Meantime, these children have been receiving all the other forms of study and treatment commonly employed in the study of bronchial asthma. While on maintenance dose therapy with ACTH and cortisone, the parents soon learn to reduce the dose to the minimum required to control the asthma with the use of accessory medications, as ephedrine, aminophylline, etc. This tends to mitigate any possible ill effects from the hormone therapy, as well as to reduce greatly the cost of treatment. Because of our preference for ACTH therapy in children

we have not used long term cortisone therapy except in one instance of eczema.

We have occasionally treated asthmatic children with intermittent courses of ACTH or cortisone and feel that this, also, is a very useful procedure. It is possible for some children to have free intervals of several weeks or even months. This method of treatment has been described in adults by McCombs (6).

Hydrocortisone may be used instead of cortisone orally in a dosage equal to two-thirds of the dose of cortisone. However, this appears to offer no special advantage other than that the child has fewer tablets to swallow.

ADVERSE REACTIONS TO ACTH AND CORTISONE

The commonest unpleasant effect of these hormones, in our experience, has been the production of varying degrees of Cushing's syndrome. This is characterized by a particular type of obesity producing the typical "moon face," the "buffalo hump" between the shoulders, and obesity of the trunk with sparing of the extremities. Other symptoms of this syndrome, as described by Plotz and associates (8), are hirsutism, hypertension, menstrual disturbances, mental symptoms, acne, pigmentation of the skin, purpura or easy bruisability, ankle edema, headache, polydysia, and polyuria.

In children we have experienced chiefly adiposity, and, to a much lesser extent, pigmentation and hirsutism. One girl developed skin lesions suggesting striae albicantes, but these disappeared on continuing the therapy. In one instance hypertension was encountered. One boy on ACTH therapy developed nephrosis, which was probably purely coincidental (4). In some instances, even in infants, euphoria has been observed. A marked increase in appetite is very common, and very distressing because of the resulting increased weight gain. We have, in such instances, used reducing diets, dexedrine and Mellozet wafers (Upjohn) with no very significant success. In every instance, all disagreeable symptoms disappeared on discontinuing the hormone therapy.

The most dangerous complication is masked infection. We have had several experiences where children on these drugs developed unrecognized fulminating pneumonia at home and were hospitalized

critically ill, and, in one instance, moribund. Fortunately, we have had no deaths as yet. This is a calculated risk on ambulatory therapy, concerning which the parents of the child should be warned. If the child acts ill or peculiarly in any way while on these drugs, the physician should be notified and, in case of any doubt whatsoever, vigorous antibiotic therapy should be started.

It is well known that latent tuberculosis may be activated by ACTH and cortisone, and this should be considered before these drugs are administered. Gastric ulcers may also occur from their use. We have had no difficulty from this source, but we have seen a few children who developed gastric distress while on these drugs relieved by alkali by mouth. Demineralization of the bones has not been observed, even with children on long-term therapy.

If, during the course of treatment with the hormones, a surgical operation is necessary, it is advisable to double the dose, starting a day previously. This should be continued until the patient is well over the shock of the operation. The dose should also be doubled in case of trauma of any marked severity due to accident or other causes. An intercurrent infection is not an indication to reduce or discontinue hormone therapy but is an indication for very vigorous anti-infectious therapy and close observation of the patient. When the drugs are discontinued, this is best done gradually.

POTASSIUM IN RELATIONSHIP TO ACTH AND CORTISONE THERAPY

As stated previously, both the Compound F-like and the desoxycorticosterone-like hormones cause increased secretion of potassium in the urine, the latter hormones being principally responsible. In maximum stimulation, there may occur sodium retention with edema and potassium deficiency. We have been particularly concerned about the possibility of this in treating very young infants and children with ACTH and cortisone because of their relatively low electrolytic reserves. It is considered important, therefore, to be able to recognize the symptoms of hypokalemia and also hyperkalemia.

Falconer and associates (3) state that the symptoms of potassium deficiency (hypokalemia) are as follows: Weakness, drowsiness, anorexia, nausea, chronic ileus with distention, edema, oliguria, and shallow, infrequent respirations. It is very easy to see how some

of these symptoms might also appear in an acutely ill infant or young child merely as a result of status asthmaticus *per se*. It is for this reason that in treating a child with relatively large doses of these hormones, as in status asthmaticus, we feel that we should have some idea as to the relative state of potassium balance in the patient.

Darrow (2), who has done much brilliant work in the study of potassium metabolism, states that when the concentration of potassium in the blood is between 3 and 4 mEq. per liter the following electrocardiographic changes are likely to develop: Slightly prolonged QT interval in relation to the PT interval; decreased height and inversion of the T waves, and rounded, prolonged T waves and possibly inversion of the P waves, extra systoles and auriculoventricular block. The prolonged QT interval seems to depend upon the prolongation of the T waves that may run into P waves. These changes are not specific since they occur in other conditions. Their association with low serum potassium is evident when the changes disappear after the serum potassium concentration is restored to normal.

Darrow states that while it is difficult, if not impossible, to produce potassium poisoning by oral administration except in patients with renal failure, shock or adrenal insufficiency, potassium intoxication can be produced by the injudicious parenteral use of potassium salts. The following symptoms have been associated with hyperkalemia: Listlessness and mental confusion; numbness and tingling of the extremities with a sense of weakness and heaviness of the legs; cold, gray pallor; bradycardia and totally irregular rhythm; peripheral vascular collapse; poor heart sounds and low blood pressure, and descending flaccid paralysis. It is obvious that many of these symptoms would be difficult to detect clinically in the child acutely ill in status asthmaticus.

As regards potassium in the blood serum, Darrow states that when this reaches a level of 6.5 to 7.8 mEq. per liter the first change is alteration of the T wave which becomes high in peak. Heart block and irregular rhythm occur at 10 mEq. or slightly higher. As the potassium increases, there is increased duration of the PR interval leading to auricular standstill, biphasic curve with progressive delay in ventricular conduction and total arrhythmia leading to cardiac arrest.

In our experience, we have never had any difficulties which might be attributed either to hypo- or hyperkalemia. However, we have had a number of instances in which the electrocardiogram showed typical evidence of hypokalemia whereas the blood potassium was normal. I feel that the electrocardiogram offers a better way of determining the potassium reserves of the body than the blood potassium level, although as yet our experience in this direction has been limited.

If the electrocardiogram shows clinical evidence of hypokalemia, then if the child cannot take potassium by mouth as discussed previously, the parenteral administration of potassium is advisable. This may be done by the use of 0.2 per cent potassium chloride in 5 per cent dextrose in distilled water, given by slow drip. Electrocardiograms should be taken at frequent intervals, say every two or three hours, in order to check on the state of the patient's potassium balance. Potassium should not be administered unless the patient is well hydrated and voiding freely.

It is more than likely, however, that the regulation of potassium metabolism is not quite as simple as indicated above. For example, Merrill (7) stated that it is possible that severe sodium deficit can imitate potassium intoxication and that the electrocardiographic signs of potassium intoxication have been reversed abruptly by the administration of concentrated sodium chloride. Myocardial infarction (certainly rare in infancy and childhood) can mimic potassium intoxication electrocardiographically. In the present light of our knowledge, we must be guided, not only by blood chemical and electrocardiographic studies, but also by the clinical condition of the patient who must be most closely watched.

EOSINOPHILIA IN PEDIATRICS

Since the Thorn (13) eosinophil depression test is so commonly used as a guide to the effects of ACTH or cortisone therapy, a short discussion of the eosinophil count in pediatrics would appear to be in order. This subject has been very thoroughly reviewed by Wolman (14) from whose article the following material is largely obtained. Wolman states that the line between normal and elevated eosinophil counts is indefinite. Most healthy children, in random tests, have absolute counts between 100 and 500 per cmm. About

600 or 700 per cmm. may be taken as the approximate upper limit of normal. This is 6 or 7 per cent of the differential when the total leukocyte count is about 10,000. It is apparent that the diagnosis of eosinophilia in childhood is made more often than is actually warranted. The absolute levels of eosinophils are unrelated to the total leukocyte counts. Because of this lack of constancy, it is important, when utilizing the eosinophil count as an indicator of adrenal cortical function, to first determine the individual's base line. No significance can be attached to changes which are not of major degree, at least 50 per cent and preferably higher in older children, or at least 35 to 40 per cent during infancy.

Eosinophilia can be demonstrated intermittently, if not consistently, during the active stages of asthma, pollinosis and atopic dermatitis. Elevated eosinophil counts are also seen in a large percentage of cases of serum sickness, angioneurotic edema, urticaria, drug reactions, periarteritis nodosa, Henoch-Schoenlein purpura and related disorders which seem to be associated with allergy. Intestinal parasites, with the notable exception of enterobiasis, also commonly produce eosinophilia.

In a fair percentage of apparently healthy children with moderate eosinophilia, no cause can be found despite intensive study for parasitism, hypersensitivity and other likely causative factors.

THE EOSINOPHIL DEPRESSION TEST

The injection of ACTH stimulates the secretion of all the known types of physiologically active adrenal cortical steroids. This response depends upon a competent adrenal cortex. ACTH stimulates the adrenal cortex directly. It is believed that the stimulus for the eosinophil decrease is the release of 11-oxycorticosteroids from the adrenal cortical cells. Epinephrine and most other drugs are believed to have their primary action on the hypothalamus; this center then activates the anterior pituitary, which, in turn, stimulates the adrenal cortex. The same pathway is believed to be operative with other stresses which evoke eosinopenia, such as surgical operation, insulin shock, burns, etc.

When the eosinophil depression test is being used as a test for adrenocortical function, the total eosinophil count is first determined with the subject in a fasting state. ACTH is injected, the dose

being 25 mg. for children, and with infants proportionately smaller amounts. The count is then repeated in four hours and the readings compared. Above infancy, a diminution of more than 50 per cent circulating eosinophils is customarily encountered when the functioning of the adrenal cortex is presumably normal; in infants the fall may be only 35 or 40 per cent. On interpreting the results, one must remember that normal persons may spontaneously exhibit oscillations of this magnitude without apparent cause. If no other approach to estimation of adrenal cortical function is being coincidentally utilized, it is wise to repeat the test at least once. A marked eosinopenia must be obtained each time before reliance can be placed on results.

The eosinophil level subsides significantly during therapy of nearly all disorders with ACTH or cortisone, and remains low until the therapy is discontinued. Complete disappearance of the eosinophils during sustained ACTH therapy is believed to be an early warning of overdosage, although this is by no means certain. Failure of eosinopenia to develop during the first twenty-four hours of ACTH treatment in suitable conditions is commonly associated with an inadequate clinical improvement.

If the eosinophil depression test is negative and it is desired to treat the allergic condition, then cortisone should be employed instead of ACTH, although even under these circumstances a clinical trial with ACTH may be successful.

The story of the steroids in the therapy of allergic and other diseases, however, may be considered as hardly more than having just begun. As this manuscript is being completed, experiments are being carried out with prednisone and prednisolone, drugs closely related to cortisone and hydrocortisone. The evidence is that they are more effective and can, therefore, be given in smaller doses than cortisone and hydrocortisone. Since their use is not associated with sodium and water retention and potassium loss it is not necessary to give added potassium or to place these patients on a low sodium and high potassium diet when these drugs are administered. Peptic ulcers, psychoses, and reduced carbohydrate tolerance have been reported following the use of prednisone and prednisolone but these preparations have not been used long enough, at this writing, to fully evaluate both their therapeutic value and the undesirable side effects which may possibly follow their use.

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CORTICOTROPIN (ACTH) AND CORTISONE IN PREGNANCY

THE PHYSICIAN dealing with the newborn infant is naturally interested in the possible effect of these hormones on the infant. As yet little information is available and this has been reviewed by Katzenstein and Morris (1). They stated that despite the adverse effect upon the offspring when the steroids are given experimentally to pregnant animals, they could find no report of damage to a baby from steroid therapy administered to pregnant women. They reviewed seven cases and presented an additional patient of their own. One of these (2) was a woman with pulmonary berylliosis who was given ACTH at the beginning of her second pregnancy and cortisone during the last eighty-seven days. She was delivered of an apparently normal child in whom severe hypoglycemia developed forty-eight hours after delivery. The child was treated with fluids and cortisone and was discharged from the hospital eleven days after birth apparently well. Whether or not the child's difficulty was due to the steroid therapy which the mother had received is problematic.

Margulis and Hodgkinson (3) reported one infant whose mother had received 5010 mg. of cortisone during pregnancy. This baby was limp and cyanotic for the first seventy-two hours with a direct eosinophil count of 1050 twenty-four hours after birth. It was suggested that the child's condition represented the effects of hypo-adrenal activity and was comparable to the effects of withdrawal of cortisone after prolonged administration. It would seem reasonable, therefore, if the mother has been receiving cortisone, to start the newborn infant immediately on a dose of 25 mg. every six hours. This is twice the dose which has been used experimentally in premature infants in the experimental and unfortunately unsuccessful prophylaxis of retrolental fibroplasia. The dose could then be gradually reduced depending upon the infant's behavior. It might

be well at the same time the cortisone is given to also administer potassium by mouth. The preparation described in Chapter 39 could be used and 5 drops be given three or four times a day.

Smith and associates (4) reported one mother who had received 100 mg. cortisone daily for two months immediately prior to delivery. A generalized acneform eruption appeared shortly after birth and the infant was given 75 mg. of cortisone the first day and 50 mg. the second day. Antibiotics were also administered. The eruption disappeared within three or four days. It is possible, though not certain, that the eruption was in some way related to the cortisone which the mother had received.

It had been hoped that cortisone might prove helpful in the prophylaxis of erythroblastosis fetalis. Wiener (5) believes, however, that there is no evidence that the drug is helpful for this purpose and therefore advises against its use.

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CHAPTER 41

POLLINOSIS

(Seasonal Allergic Rhinitis; Tree Pollinosis; Rose Fever; Hay Fever)

POLLINOSIS is by far the best known form of allergic rhinitis. The exact incidence of this disease in children in the United States is not known. This will probably vary in different localities with the amount of pollen commonly present. In Rochester, New York, where the average ragweed pollen index, as determined by the method of Durham (10) for eight consecutive years up to 1948 inclusive, was 59, Glaser (12) *et al.*, in a study of ragweed pollinosis in school children, found the incidence to be 5.5 per cent in 1366 grade school students and 13.3 per cent in 774 high school students. The schools in New York State commonly open the first Monday after Labor Day, which usually coincides with the height of the ragweed pollen season. This study was made in an effort to determine whether a sufficient number of school children suffered from this disease to justify the postponing of the opening of school at least a week until the height of the season was past. Despite evidence to this effect, no action has as yet been taken by the school authorities.

The age of onset is also probably directly related to the quantity of pollen in the air. Over a twenty-year period in Rochester, New York, the earliest onset I have observed was in the case of two infants, each six months of age. They were treated symptomatically the first year and specifically after the symptoms recurred at the age of eighteen months, at which time definitely positive scratch tests to ragweed pollen were elicited. London (18) described a four-month-old boy in New Jersey with hay fever who reacted on scratch tests to ragweed and cocklebur. This patient's symptoms were completely relieved by pollen extract injections and did not recur thereafter. In the one of my cases which I was able to follow, with the

onset at the age of six months, the girl still required injections of pollen extract at the age of eighteen years. Kahn (16) infers that in Texas newborn infants may, in rare instances, develop symptoms of hay fever shortly after birth. Shuller (27), practicing in the same part of the country, finds hay fever a common condition in children under two years, and believes that it may have its beginning at the age of only a few days or weeks.

Clarke and Leopold (5) note that the onset of hay fever is earlier in boys than in girls and that during the first decade more boys have hay fever than girls. This had been previously observed by Nelson (21), who reported that males dominate in the proportion of two to one in the first decade and females predominate in the second and third decades. The former authors suggest that young boys are more apt to get hay fever than girls because of their greater exposure to pollen; they are more likely to roam and play in the fields than are their sisters.

SYMPTOMATOLOGY

Usually pollinosis may reasonably be considered if, during the pollen season, a child has an attack of sneezing, running nose, itching nose, conjunctivitis, itching eyes or cough, or any combination of these symptoms. Commonly, at first, a "cold" is suspected. Usually inspection of the nose is sufficient to establish the diagnosis. The turbinates are pale, edematous and moist, and the discharge is serous or mucoid. In the case of an ordinary coryza, the turbinates are red, not swollen, and the discharge is commonly mucopurulent. If there is doubt regarding the diagnosis, a nasal smear for eosinophils stained according to the method of Hansel (13) will usually, though not always, establish the diagnosis by showing a preponderance of eosinophils in the case of allergic rhinitis and polymorphonuclear leukocytes in the case of coryza. Mixed types of smears may occur because of superimposed infection.

Occasionally pollinosis will affect only the mucous membranes of the eyes, causing conjunctivitis, without other evidence of pollinosis, or the mucous membranes of the bronchial tree, causing cough or asthma, also without other evidence of pollinosis. The recurrence of the symptoms from year to year, always at about the same time, makes the diagnosis of pollinosis almost positive.

INDICATIONS FOR SPECIFIC TREATMENT

One of the most difficult problems confronting the pediatrician caring for a child just starting to suffer from pollinosis is when to start specific treatment by the injection of pollen extract. Certainly a large percentage of individuals with pollinosis later develop bronchial asthma. Vander Veer (29) estimates that about 30 per cent of untreated hay fever patients develop seasonal asthma. Peshkin (23) noted that 60 per cent of children with pollinosis observed by him subsequently developed asthma. MacKinney and Glaser (19), in a series of 141 children with pollinosis, most of whom had specific treatment, observed that 25.5 per cent developed asthma at an average period of two and one-half years after the onset of the pollinosis. It seems reasonable to suppose that the incidence of subsequent asthma is less in patients who have had the injection treatments. Walzer (33) states, and I also feel, that patients with pollinosis should take the injection treatments, regardless of how little the symptoms appear to be helped, since this is the best weapon we have to combat the development of pollen asthma, and this is especially true in children. Criepp (9) also noted that the treatment of pollinosis is an effective prophylactic measure against the development of bronchial asthma. According to Waldbott (31), Duke, in 1924, recognized ragweed pollen as the most important single cause of chronic asthma. In 1933, Waldbott (32) demonstrated that most perennial asthma originates from pollen, especially from ragweed. My own experience is in accord with this. It would, therefore, appear that the occurrence of pollinosis *per se* is a positive indication for treatment, regardless of the mildness of the disease or the age of the patient. There is, further, no evidence that properly administered pollen therapy can increase a child's sensitivity to pollen.

As a practical consideration, it should be explained to the parents that, in the case of mild pollinosis, not a great deal of improvement may be expected since, as a rule, the worse the pollinosis the more striking is the improvement on specific therapy. If the child exhibits only slight symptoms in an unusually severe pollen season, it may be justifiable to treat the pollinosis only symptomatically in the hope that the condition, in successive seasons, may be less severe. Specific therapy may be unnecessary or delayed until the child is older and treatments are less disagreeable, both to the child and to the parents.

At present, I am guided by the following as indications for treatment:

1. Progressive increase in severity of symptoms from year to year.
2. Symptoms sufficiently severe to be annoying and require frequent symptomatic treatment for relief.
3. Persistent cough—invariably a forerunner of asthma.
4. Asthma—an absolute indication.

MASKED POLLINOSIS

This clinical entity occurs in only a limited number of individuals. It is most commonly due to ragweed pollen, but the patient has no signs of pollinosis during the ragweed pollen season. After the season is past, the patient has considerable difficulty through the fall, chiefly with "sinusitis," recurrent upper respiratory infections, bronchitis and sometimes asthma. On skin testing, large reactions to ragweed pollen are commonly obtained and the patient often does remarkably well on treatment with ragweed pollen extract only.

This condition was discovered quite by accident in a physician whose sons were under my care because of nasal allergy. He had, for years, been hospitalized for several weeks every fall with chronic nasal difficulty, diagnosed as "sinusitis." He requested that I skin test him and, on so doing, he reacted only to ragweed. He was treated with this with complete success, and has not suffered since from the previous complaints. This stimulated my interest in the condition and I have since discovered a number of other patients with the same difficulty who also responded well to similar treatment. Although this occurs at the beginning of the "house dust season," it is not due to house dust, but responds specifically to treatment with pollen.

A possible explanation of the mechanism of this is as follows. The nasal membranes of such patients suffer subclinical injury during the ragweed pollen season. The patient may have wide nasal passages in which edema and swelling pass unnoticed. Another individual with the same amount of nasal involvement, but with narrow nasal passages, might experience considerable difficulty under exactly the same circumstances. When fall approaches with its changeable weather, the damaged membranes of the patient with masked pollinosis cannot adjust to this; the membranes are easily infected and the above symptoms result.

SKIN TESTING WITH POLLEN EXTRACTS

The pollen extracts with which a patient should be tested will vary from one part of the country to another. Detailed studies concerning this will be found in the works of Coca, Walzer, and Thomsen (6), Vaughan (30) and Cooke (7), and need not be repeated here. Considerable valuable information may also be obtained from the publications of the various commercial houses selling pollens or pollen extracts. It is necessary for the pediatric allergist to be familiar with the common pollen producing flora in his own locality. In certain areas, mold spores may also play a role. If the patient has typical pollinosis, it is not my custom to do complete testing with all allergens, as, for example, in the case of a patient with perennial asthma. The patient is tested with pollens prevalent in my locality and, in addition, the common foods, eggs, wheat, milk, and a few other important allergens, as house dust, feathers and wool, and any other allergens which might be indicated by the history. All testing is done by the scratch method, followed by intradermal testing if the scratch tests are negative.

It is a matter of common observation, first reported by Kahn and Grothaus (16) in 1925, that the skin tests may be negative in typical pollinosis. In such cases, the child may commonly be successfully treated on the basis of the history alone with the pollen extracts of the pollens commonly producing symptoms in that particular locality at the time the child suffers. If it is necessary to demonstrate a positive test in order to convince a doubting parent, the dry pollen eye test devised by Peshkin (22) is most useful. The test is done by simply dropping the natural dry pollen into the conjunctival sac of one eye, using as a control pine pollen instilled similarly into the conjunctival sac of the other eye. If the conjunctiva is sensitive to the test pollen, it will react with varying degrees of congestion and edema. The reaction may be easily checked by carefully removing the pollen from the eye with a cotton-tipped applicator and instilling one or two drops of epinephrine 1/1000. The test may be done in children as young as four years, and even younger if they will cooperate. It is not necessary, as some allergists have stated, to do the test with dilutions of pollen extract of gradually increasing strength. It is also true that a negative pollen eye test does not rule out pollen as a cause of the patient's symptoms.

TREATMENT BY THE INJECTION OF POLLEN EXTRACTS

Treatment with pollen extract is started with 0.10 cc. of the dilution, one-fifth in strength of the strongest dilution which does not give a positive skin test. For example, if the patient's skin did not react on scratch testing to a 1/62,500 dilution and did to a 1/12,500 dilution, his starting dose would be 0.10 cc. of the 1/62,500 dilution. If the scratch tests are negative, the starting dose is 0.10 cc. of the 1/12,500 dilution, although much higher starting doses are doubtless quite safe, as indicated by the report of Levin (17).

There is great divergence of opinion concerning maximum dosage between the various authorities on treatment with pollen extract. While Hansel (14) uses doses of miniscule proportions, others, like G. T. Brown (4), appear to have no hesitation in treating with the strongest extracts available. Ratner (26) occupies a middle ground with a dose not exceeding 0.30 cc. of a 1/5000 dilution. All this is bewildering and, as yet, not completely explicable, not only to those first starting to work in allergy, but also to those who have worked in the field for a long time. My opinion is that, in every instance, the dose must be determined for each individual. In some cases, a very small dose will prove satisfactory; in others, one must use an exceedingly large dose. The great majority of cases will naturally fall somewhere in between.

It is quite possible, also, that there are local differences relating to the amount of pollen in the air, its degree of toxicity, and probably still others, as yet unknown, which will determine the average maximum dose. In Rochester, New York, my maximum dose rarely exceeds 0.50 cc. of a 1/250 dilution. For a very fine discussion of dosage in the treatment of pollinosis with special reference to the fallacies of extremely low dose therapy, reference is made to the study of Mueller (20).

A phenomenon occasionally noted is that a patient who, for example, is well tolerating a dose of 0.50 cc. of a 1/250 dilution, may suddenly begin to give severe generalized reactions to this dose. It then becomes necessary to reduce the dose to an amount well tolerated by the patient, for instance 0.50 cc. of a 1/2500 dilution. The patient commonly does just as well on smaller doses as he did on the larger, which lends some credence to the rule employed by some, and credited by Abramson (1) to Rockwell, to the effect that

the maximum dose of pollen tolerated by the patient is also the optimum dose for that patient. The phenomenon just described of sudden change of tolerance for a given dose is much more frequently observed in adults than in children.

If a patient is sensitive to house dust or molds, he is concomitantly treated with these extracts. If he reacts to feathers and other allergens, instructions are given for specific avoidance. If the patient does not respond satisfactorily to treatments, complete skin testing is subsequently carried out.

Most patients start treatment several weeks before the onset of the pollen season for which they are to be treated. This is known as the preseasonal method of treatment and the schedule which I employ is shown in Table XIV. Occasionally it appears advisable to start a patient on treatments during the pollen season, i.e., coseasonal therapy. For this purpose, the intradermal method of administering pollen extract, as first advocated by Phillips (24, 25), is the method of choice. Small doses of pollen extract, 0.10 to 0.15 cc. are given intradermally at one to three-day intervals. The strength of the solution employed is that which will give a wheal about 1.5 cm. in diameter, if that dose also appears to give the best clinical results. Intradermal injections of part of the mixture are also employed during the season with any patient who is not responding satisfactorily receiving injections of pollen extract. In some instances, this appears to afford better relief than the subcutaneous injection of pollen extract.

I most commonly employ the perennial method of treatment. This procedure, which was popularized by Aaron Brown (3), consists of continuing the injections after the pollen season has passed. The treatments are given at intervals gradually increased by increments

TABLE XIV

Dr.	Date
Patient	
Schedule of Dosages for Treatment with	

(Please read special direction sheet before any injections are given.)

The treatments are to be given regularly each week until the maximum dose is reached when they are to be continued at intervals.

START WITH THE DOSE INDICATED BY THE ARROW. On reaching Solution No. 0.05 cc. of epinephrine (adrenalin) 1:1000 is to be added to each dose as indicated in paragraph 4 on the special direction sheet. This may be omitted if it causes undue nervousness or tremor.

Each solution is five times the strength of the preceding solution. Unfavorable reactions may prevent advancing the patient as rapidly as indicated in the following schedule. *It may be necessary to go back to a well tolerated dose and increase by smaller increments than indicated in this schedule.* This depends upon the judgement of the attending physician.

(Table continued on next page)

of one week until the patient gets an injection every three or four weeks. Commonly, the maximum dose attained may be continued by this method, but, if not well tolerated, the dose must be reduced to the point of satisfactory toleration. Weekly injections are resumed with the beginning of the next pollen season. Using this method, many patients experience the same or better relief than with other methods of treatment. In many instances the number of injections required will be greatly reduced. However, the method of choice is that which gives the best results in any particular instance.

It is a matter of common observation that the dose of pollen extract necessary for infants and children has no relationship to age or weight. An infant may, at times, require a dose infinitely larger than that required by an adult. Age, also, is no contraindication. No child is too young to be treated by the injection method for pollinosis.

It is a well known folk observation that some patients with pollinosis are made worse by the ingestion of particular foods which can often be eaten at other times of the year with immunity. Walzer (33) regards this as the commonest cause of failure in the treatment of pollinosis next to the improper use of pollen solutions. He states that the most common ingestants contributing to such failure are alcohol, corn, cherries and chocolate. This is true whether or not these patients react to the substances by skin test. I have not observed this phenomenon in children, but it could be easily overlooked as children and their parents would not be apt to notice a causal relationship between the increase of their hay fever symptoms and the ingestion of food as readily as would be expected of an adult.

The same precautions for the injection of pollen extracts must be observed as those used for the injection of all other allergenic extracts. Specific directions for the administration of pollen extracts are noted in Table XV.

The problem naturally arises as to how long the pollen treatments should be carried out. It is my practice to treat the patient until he has been completely symptom-free through one fairly severe pollen season. This means that, during that season, the patient should have no symptoms of pollinosis whatsoever. Under such circumstances, patients discharged from treatment will sometimes remain permanently "cured." Occasionally the pollinosis will recur after a lapse of one or several years. This seems to depend largely upon the severity of the exposure to pollen. Many of my former child patients

TABLE XV

PRECAUTIONS FOR INJECTION OF POLLEN SOLUTIONS

1. Treatments are preferably administered by a licensed physician. Treatments given by others are at the patient's own risk.
2. Keep all solutions in the dark in a refrigerator.
3. Never give an injection unless you have on hand a vial of epinephrine hydrochloride (adrenalin) 1/1000 for use in case of a pollen reaction.
4. With each dose of pollen extract, starting with Solution No. always give 0.05 cc. of adrenalin mixed with the pollen extract in the same syringe. In other words, draw into the syringe 0.05 cc. of adrenalin and then draw into the same syringe the dose of pollen to be administered.
5. The skin is to be cleansed with 70 per cent alcohol before injection; 1cc. Luer tuberculin syringe should be used and all injections should be given subcutaneously. ALWAYS PULL BACK THE PISTON OF THE SYRINGE BEFORE AN INJECTION OF POLLEN SOLUTION. If blood appears in the syringe, always change the position of the needle point to make sure that the solution is not injected into a blood vessel.
6. Always keep the patient under observation for one-half hour after an injection. Overheating, as from exercise, should be avoided.
7. If a pollen reaction occurs (usual manifestations—urticaria or an acute attack of hay fever or asthma, cyanosis, flushing, perspiration, nausea, vomiting, dizziness, fainting or collapse) place a tourniquet around the patient's arm above the site of the injection and inject $\frac{1}{2}$ cc. of adrenalin into the site of the pollen injection. Repeat the adrenalin as necessary and release the tourniquet occasionally so that you do not embarrass the circulation. SUBSEQUENT DOSES MUST BE REDUCED. Give 100 mg. of cortisone orally or by injection or 40 to 80 units of aqueous ACTH as soon as possible after the onset of a severe reaction.
8. If the patient gives reactions frequently, it is well to place a tourniquet around his arm prior to giving the injection and give this below the tourniquet with the tourniquet still in place. Then the tourniquet may be released at intervals, thus permitting slower absorption of the pollen.
9. If the patient experiences trouble because of the injections such as sore arms or more general forms of reactions, it may not be possible to proceed as rapidly as indicated in the schedule. Under such circumstances it is better practice to go back to a well tolerated dose and to increase, if possible, by smaller increments than those originally suggested. On the contrary some patients may be able to tolerate more rapid increases than those indicated in the schedule. This depends upon the judgment of the attending physician.

DO NOT REMOVE STOPPERS FROM BOTTLES

who had been discharged as "cured" and were later, as young men, inducted into the infantry during the war, had a recurrence of their symptoms when exposed to excessive pollen in the course of their training. Tuft (28) also feels that a patient should be treated for pollinosis until a complete remission has occurred for one year. Skin tests are not a criteria. He then tests the patient by instillation of pollen into the nose. If no symptoms appear the patient is discharged. He does not retest a patient each year while under treatment, if his progress is satisfactory, unless he is taking preseasonal and not perennial treatments. This, also, is my practice.

Biederman (2), in 1935, observed that, of patients who react positively to pollen of one season and have symptoms, but who also have a skin sensitivity to pollens of an additional season, approximately 5.5 per cent will develop symptoms to the latter the following year. If, however, the extract of this pollen is administered

before symptoms from it arise, then they may not appear, or appear only mildly. I have followed Biederman's suggestion with satisfactory results, and have extended it to the point of giving pollen extract to allergic children being treated by injection for any other allergic condition, as a prophylactic measure against the development of pollinosis. Tuft (28) also employs the same procedure. While no control studies have been made, I have the impression that it is effective. It seems a very reasonable thing to do.

THE SYMPTOMATIC TREATMENT OF POLLINOSIS

This is of great importance as the specific treatment probably gives completely satisfactory relief only in about 75 to 85 per cent of cases. Many of the symptoms of pollinosis may be relieved by the antihistaminics, and for a discussion of these drugs reference is made to Chapter 47. Occasionally, when these fail or are not tolerated, atropin sulphate, in appropriate doses, usually 0.065 mg. (1/1000 of a grain) or 0.13 mg. (1/500 of a grain), will often prove useful. However, if atropin dries the throat before it dries the nose it will not prove satisfactory for relief of the nasal symptoms. Unlike the antihistaminic drugs, which are occasionally successful, atropin will not relieve nasal obstruction. Quite frequently nose drops will reduce nasal obstruction where other measures have failed. The proper method for the instillation of nose drops has been previously described (see Chapter 36). If the nasal obstruction is so extreme that drops cannot be instilled, the procedures mentioned in Chapter 36 should be tried. Where other nose drops have failed, I commonly advise the instillation of Privine nose drops (0.05 per cent—Ciba) (see also Chapter 36) at bed time and once during the night if awake, and the instillation of the milder vasoconstricting nose drops (ephedrine or neosynephrin) on arising in the morning and before lunch and supper.

For the relief of eye symptoms, drops containing ephedrine* are

* Wyeth's Collyrium Eye Drops with Ephedrine are satisfactory in the great majority of cases. This is an isotonic solution of boric acid and borax, containing 0.4 per cent antipyrin and 0.1 per cent ephedrine. Another preparation commonly used is the Antistine-Privine eye drop of Ciba, which contains 0.5 per cent antistine hydrochloride and 0.025 per cent privine hydrochloride in an isotonic aqueous solution buffered to a stable pH.

often useful. If these do not help, the prescription recommended by Cooke (8) is very helpful:

Cocaine hydrochloride	0.1
Boric acid	1.0
Epinephrine hydrochloride	8.0
Rose water qs ad	32.0

Mix and label: Eye Drops

Sig.: Instill 1 or 2 drops into each eye.

All other measures failing, cortisone eye drops should be tried.

Itching of the throat may be alleviated by the use of anesthetic lozenges. The troches of Anesthesin-Calcidin, of Abbott,* are quite satisfactory, but there are many others, equally useful, on the market.

ACTH and cortisone have recently proven of great help in the symptomatic treatment of otherwise uncontrolled pollinosis. It would seem that cortisone, since it acts so well orally, would be an ideal method of treatment. Whether or not this will prevent the ultimate progression of pollinosis into asthma awaits experience certain to be gained the next few years. Experience thus far indicates that it cannot be expected to replace specific therapy.

Air conditioning is increasing in use for cleansing the air of pollen since it has become more efficient and less expensive. There are now many satisfactory pieces of apparatus which can be installed in almost any room for the purpose of cleaning, cooling and dehumidifying the air. Filters are also available without cooling devices, and these are much less expensive.

Finally, it is highly desirable to advise all patients to plan to take their vacations during the height of the ragweed pollen season, in Rochester, New York, usually the last week in August and the first week in September, in localities relatively free from pollen. The booklet by Durham (11) is of great assistance in selecting such localities.† For people who suffer from cold and dampness in mountain resorts, the east coast of Florida is recommended. Hotel rates

* Each contains 15 mg. (1/4 grain) of the local anesthetic, Anesthesin.

† This may be obtained gratis by writing to Mr. O. C. Durham, Chairman, Pollen Survey Committee of the Research Council of the American Academy of Allergy, Abbott Laboratories, North Chicago, Illinois.

TABLE XVI*

RAGWEED POLLINOSIS (HAY FEVER)

GENERAL DIRECTIONS

Your difficulty is due to the pollen of the ragweed plant. In this locality it pollinates from the middle of August until about the first of October. The height of the pollination season is generally reached about the last day of August or the first three days of September. If possible, you should arrange to take your vacation in a pollen free area, as the Central Adirondacks, the last week in August and the first week in September so as to escape the height of the ragweed pollen season. **THIS SHOULD BE DONE EVEN IF YOU TAKE THE INOCULATIONS** as these rarely give 100 per cent relief.

From the middle of August to the end of September the following precautions should be observed:

1. Sleep with your windows closed as far as possible. If it is necessary to have an electric fan going, have it placed so it blows *out* of the window. Filters which will take the pollen out of the air and at the same time cool the room are expensive but very much worth having. Less expensive filters which do not cool are also available. A simple filter of this type may be built at home from directions which will be given upon request.

2. Stay indoors on windy days. Avoid drafts and cross ventilation.

3. Avoid long automobile drives; do not drive at all unless absolutely necessary and when you do, drive with the windows closed if possible. If not possible, avoid cross drafts while driving. If you must take long drives, wear a mask.

4. Avoid members of the ragweed family or plants. Do not smell, pick or carry these flowers or permit them in your house at any season of the year:

Asters	Dandelions
Bachelor's buttons	Gaillardias
Calendulas	Goldenrod
Chrysanthemums	Marigold
Coreopsis	Pyrethrum
Cosmos	Sunflower
Dahlias	Zinnias
Daisies	

5. Avoid all strong odors as they act as non-specific irritants. Especially bad are strong perfumes; fresh paint; gasoline; tobacco smoke.

6. Do not drink ice cold beverages or eat ice cold foods.

7. All individuals, and particularly allergic individuals, should be immunized against tetanus so that if injured tetanus antitoxin, which is especially likely to cause trouble in allergic individuals, will not be required but instead merely a booster dose of tetanus toxoid.

8. The pollen injections should be continued until you have had one year with a fairly bad pollen season absolutely free from symptoms.

* Reproduced by courtesy of Dr. Bernard G. Efron, modified to fit local conditions in Rochester, N.Y.

are at their minimum at that time, and, if one stays close to the sea shore, the heat is not unbearable.

I also issue to my patients with ragweed pollinosis an instruction sheet devised by Dr. Bernard G. Efron of New Orleans and reproduced here with his permission (see Table XVI). This has been found most helpful.

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LESS COMMON DISEASES DUE TO POLLEN

VULVO-VAGINAL PRURITIS

IN 1948, Mitchell and associates (8) described vulvo-vaginitis due to pollen as a new entity. Eight cases in children four to eleven year of age were reported. In each, the history of vulvar itching was voluntarily given as a major complaint. There were no visible local changes except those as the result of the scratching. The most intense itching seemed to be in the region of the mucocutaneous junction between the vulva and vagina. Itching occurred only during the ragweed pollinating season except in three instances: in one case there was itching during the grass pollen season; in another, following the administration of a sulfonamide, and in another, after playing with dandelion blossoms. All eight of these patients also had hay fever. The authors noted that the vulvar itching responded as readily as hay fever to specific hyposensitization or avoidance of the offending pollen and that pre-seasonal pollen therapy prevented the vulvar itching in most cases.

One hundred adult female patients treated for ragweed pollinosis were questioned but no instance of vulvar itching was discovered. Thomas and Wicksten (14), however, noted a fifty-year-old woman with seasonal leucorrhea associated with ragweed pollinosis and asthma. There were no symptoms except during the ragweed season. She reacted to the local application of ragweed pollen to the vaginal mucosa. As far as boys are concerned, no cases of pruritis of the urinary meatus were observed.

Mulligan (9) reported a case of vulvo-vaginitis in an eight-year-old girl where the pediatrician suspected enterobiasis (pinworm infestation). A consulting dermatologist agreed with this diagnosis but the usual methods of treatment were of no avail. The child had mild pollinosis and because of this and the seasonal incidence of the genital itching, it was suspected that ragweed pollen might be a possible cause. She was therefore treated by the injection of ragweed

pollen with very excellent results as regards the local itching. Mulligan further observed that the application of a 1/100 ragweed solution to the genitalia produced itching and ragweed ointment caused intense itching and local reaction. These tests were not done during the pollen season when the genitals were normally inflamed.

We have observed two such cases in our own practice, one of which showed eosinophils in a smear of the vaginal mucus. We were also able to diagnose one case by mail for a physician who wrote in regard to this condition.

DERMATITIS DUE TO POLLEN

It is now well known that dermatitis of the contact type may be produced by pollen. In most instances, this is due to the oily fraction of pollen as was demonstrated by Brown (1). This is similar in nature to the dermatitis produced by poison ivy. I have seen several such cases in children. They are very rare and are best treated by the oral administration of graduated doses of the pollen oleoresin.* Extreme care must be exercised to avoid an overdose as this greatly intensifies the rash.

Shelmire (11) showed that the pollen of weeds contains both an oleoresinous fraction capable of producing a contact dermatitis and a water-soluble albuminous fraction which may cause pollinosis. It is less well known that this latter fraction may on occasion also cause atopic dermatitis, in which case the lesion is commonly produced either by inhalation of the pollen or injection of the pollen extract. A few such cases have been reported by Cunningham and Wolfe (4), Chobot (3) and by Mitchell and Mitchell (7). These have all been in adults. In infants and children it is well known that atopic dermatitis commonly tends to be worse in winter and better in summer. There are, however, a few instances in which the reverse is true. It is quite possible that some of these represent atopic dermatitis due to the water-soluble fraction of the pollen.

URTICARIA DUE TO POLLEN

G. T. Brown (2), in 1929, was apparently the first to report a patient with urticaria due to pollen. This was an adult who in addi-

* Treatment sets for this purpose may be obtained from the Graham Laboratories, Willow Lane, Route 7, Dallas 6, Texas.

tion suffered from pollen dermatitis. Both the urticaria and the dermatitis were due to grass pollen and neither responded to treatment with aqueous grass pollen extract. The following year Taub and White (12) described a young woman with urticaria due to grass pollen who, however, had not yet received specific treatments. Waldbott and Merkle (15), in 1952, discussed this problem and tabulated a list of twenty-six patients in whom the clinical evidence pointed to pollen of various kinds as the principal causative factor. In twelve the urticaria was confined to the pollen season. The two youngest patients were an eleven-year-old girl in whom the urticaria was seasonal due to grass pollen and a thirteen-year-old boy in whom grass pollen was one of the factors causing urticaria. In general, treatment was effective although difficult to evaluate.

MISCELLANEOUS CONDITIONS DUE TO POLLEN

Kahn (6), in 1927, reported a syndrome in children suffering from pollinosis characterized by anorexia, lassitude, irritability, and occasionally other symptoms, such as enuresis, which he attributed to toxemia due to the pollinosis and which could be designated pollen toxemia. He considered that other inhalants, particularly feathers, were sometimes factors but could not incriminate foods in any instance. Horesh (5), also, has reported on pollen as a cause of fatigue, restlessness, dullness and loss of ambition. The syndrome described by Kahn is now well known and occurs not only with pollinosis but with other forms of allergy, especially food allergy. The only satisfactory treatment is that directed towards avoiding the allergen or hyposensitization. (For a further discussion of allergic toxemia see Chapter 56.) Rowe (10) has reported seasonal colitis due to pollen (see Chapter 56). Thoma (13) has published illustrations in color of one adult with gingivitis and one with stomatitis, in each instance seasonal in character and due to ragweed pollen.

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RECURRENT UPPER RESPIRATORY DIS- ORDERS OF ALLERGIC ORIGIN AND PERENNIAL ALLERGIC RHINITIS*

IT IS NOT a matter of common knowledge among physicians, including pediatricians, that the child with a frequently recurring or even apparently "continuous" upper respiratory infection or "cold" in most instances suffers from allergic nasal mucous membranes. This is not to say that there are no other causes for this condition, as will be discussed subsequently. The recurrent upper respiratory disorder or infection involving allergic nasal mucous membranes, hereinafter designated as the RURI, is one of the most important, least understood and consequently most neglected of the allergic diseases of infancy and childhood. In the series of 516 consecutive allergic children studied by MacKinney and Glaser (14) the incidence of RURI was 31 per cent, and ranked fourth in the list of incidence of frequency of allergic diseases in infants and children ten years of age or less when first seen. Asthma occupied first place with an incidence of 53 per cent.

The RURI occurs about one-third as often in adults, having been noted in 10 per cent of 200 successive adults seen in consultation and studied for the purpose of comparison. Clein (3) apparently did not differentiate this disease from perennial allergic rhinitis in his report on the incidence of allergic disease in 100 allergic children and neither the RURI nor perennial allergic rhinitis is mentioned in the series of 250 allergic children reported by Ratner and associates (17). The RURI was also not discussed in Peshkin's (16) more recent monograph. This disease is nevertheless of great importance in pediatric practice, not only because it is a great nui-

*The material for this chapter is largely taken from another publication by the author on the same subject (9) and is here reproduced with permission of the copyright owners.

sance but also because it is a not uncommon precursor of bronchial asthma.

Probably the first to truly evaluate the importance of the RURI in infancy and childhood with respect to allergy were Cohen and Rudolph (5) in 1931. This disease must particularly be differentiated from the common cold and other forms of infection of the upper respiratory tract such as rhinitis, sinusitis, nasopharyngitis, laryngitis, tracheitis, and bronchitis. Cohen and Rudolph pointed out that disorders of the upper respiratory tract in children may be divided into three classes, namely, allergic, infectious, and combined allergic and infectious. The symptoms of all three are similar and are commonly associated with infections of the nose, nasopharynx, pharynx, etc.

Other conditions which may be responsible for or are often mistakenly blamed for the RURI are infected tonsils and adenoids which are relatively infrequent offenders. In this connection it is probably accurate to state that any child three years of age or less, whose tonsils and/or adenoids are removed because they are suspected of causing this condition, is nearly always an allergic child (8). The same is true of any child who has required removal of the tonsils and/or adenoids more than once. Organic defects, such as a deviated nasal septum causing interference with sinus drainage, chronic sinus infection or infection of recurrent lymphoid tissue in the nasopharynx following adenoidectomy with organisms highly resistant to treatment, and any organic cause of respiratory obstruction in the young infant, may also simulate the RURI.

Among other less common disorders associated with frequent upper respiratory disorders are Kartagener's syndrome (see Chap. 57) and a quantitative (and perhaps qualitative) deficiency of the gamma globulin of the blood, first described by Bruton (2) and most frequently termed agammaglobulinemia although hypogammaglobulinemia would perhaps be more nearly accurate. The literature of this subject has been concisely reviewed editorially in the *Journal of the American Medical Association* (7).^{*} Curiously, Janeway and associates (13) have also shown that some children who suffer from chronic upper respiratory infections may actually have a hypergam-

^{*} Brief reference to this condition has been made in Chapter 36.

maglobulinemia. In a group of four such children, several of whom had been previously suspected of suffering from agammaglobulinemia, the serum concentration of gamma globulin ranged from 1.9 to 4.5 gm. per 100 cc. as compared with normal values in the same age group of 0.6 to 0.9 gm. per 100 cc. While it is evident that much remains to be clarified in the relationship of gamma globulin to infection, a possible deficiency of gamma globulin should be considered in the case of the child suffering from chronic, recurring upper respiratory infections, particularly if all other etiological factors, including allergy, can be ruled out. If the recurring infections appear to be due to lack of gamma globulin, Janeway and associates (14) recommend the injection of 0.10 gm. of pooled normal human serum gamma globulin per kg. of body weight every four to six weeks, and it appears to be necessary to reach blood levels of 0.10 to 0.15 gm. per 100 cc. in order for this to be effective. Dixon and associates (6) stated that in adults, whose gamma globulin half life may be less than that in children, treatments may be needed more frequently.

The pathological physiology of the RURI is the rapid onset of allergic edema of the nasal mucous membranes so that the resulting symptoms are similar to the first stage of an ordinary coryza, i.e., sneezing and nasal discharge. If the attack can be aborted at this stage, it will be of very short duration. Unless this is done, the edematous mucous membranes become secondarily infected so that the process further resembles an ordinary coryza. For this reason the term, "recurrent upper respiratory infection of allergic origin" (RURI) is commonly used although the words "of allergic origin" are commonly omitted. Infection is, however, not the primary cause of the condition which, as stated, is due to recurrent allergic edema of the nasal mucous membranes.

Cohen and Rudolph (5) published a summary of the differential diagnosis here reproduced in Table XVII. This should be studied very carefully. So thorough was their work that in the intervening years, I have been able to add to their observations only the fact that the diagnosis of this disorder can almost always be made by the history alone. Usually the description of the chief complaint by the mother is sufficient to make the diagnosis in the great majority of cases. She commonly states, "Doctor, my child has one cold after

TABLE XVII
DIFFERENTIAL DIAGNOSIS OF ALLERGIC AND INFECTIOUS CONDITIONS
OF THE UPPER RESPIRATORY TRACT IN CHILDREN

History	
Allergic	Infectious
1. Attacks usually recurrent.	1. Attacks usually single.
2. Often mild symptoms between attacks.	2. Usually clears up completely.
3. Definite relation to heredity.	3. No relation to heredity.
4. Not contagious.	4. Contagious
5. Not related to exposure to another case.	5. Definite relation to exposure to another case.
6. Constitutional symptoms slight.	6. Constitutional symptoms more marked.
7. Foods and inhaled substances often traced as causes.	7. No relation to foods or inhaled substances as cause.
8. Itching common.	8. No itching.
9. Wheezing common.	9. No wheezing.
10. Other allergic conditions present or in past history.	10. Usually no other allergic condition present or in past history.
Examination	
Allergic	Infectious
1. Visible mucous membranes, pale, glistening, edematous.	1. Visible mucous membranes, hyperemic, red.
2. Thin watery mucoid nasal discharge, mucoid sputum.	2. Mucopurulent or purulent nasal discharge and sputum.
3. Smear shows eosinophils 10 per cent or more.	3. Smear shows polymorphonuclear neutrophils as predominant cell; eosinophils few or absent.
4. Other signs of allergy often present.	4. No other signs of allergy.
5. Sinus involvement of hyperplastic type.	5. Sinus involvement of purulent type.
6. Wheezing breath sounds.	6. No wheezing breath sounds.
7. Roentgenogram shows bronchial markings increased.	7. Bronchial markings not increased in roentgenogram.
8. Allergic skin reactions usually positive.	8. Allergic skin reactions usually negative.

Combined
Allergic and Infectious

Primary allergic conditions are often secondarily infected. Cure depends on recognition and relief of the allergy. The body then overcomes the infection in most cases. This does not preclude treatment for the infection when indicated.

From Cohen and Rudolph (5).

another," and she may add, "all year long," or "all winter long" or some other modification of a similar character. In contrast to this, in Rochester, New York, the average child has three colds a winter, usually one severe and two mild, lasting on the average of a week to ten days. Individuals having more colds than this must be suspected of suffering from the RURI of allergic origin or some other disease which has to be differentiated from this condition.

Very often these children are brought to the physician's office in desperation. The child's tonsils and adenoids have been removed; he has taken vitamins to the point of saturation "to build up his resis-

tance"; long hours and many months have been spent haunting the office of the nose and throat specialist for various types of intranasal treatment, lamp treatments, etc., all to no avail. In all fairness to the nose and throat specialists, however, it may be said that they are gradually coming to recognize this disease and in Rochester, at least, many of these children are now referred to the allergist.

The diagnosis of the RURI is confirmed by the finding of an eosinophilia in a nasal smear. The technique for making such smears has been described in Chapter 28. The slides are then stained by the method of Hansel (10) and may be compared with his illustrations in color (11) which depict the various types of smears which may be encountered.

The use of the Hansel stain* is now such a fundamental and frequent procedure that it is felt advisable to describe the technique at this point:

1. Dry the smears in air or gently over a flame.
2. Cover completely with Hansel's stain and allow to stand thirty to forty-five seconds, giving the longer period of time to thicker or milky smears.
3. Add distilled water to take up the stain as in Wright's technique and allow to stand thirty seconds. Pour off the stain and flood slide with distilled water to remove excess stain.
4. Flood slide with 95 per cent ethyl or methyl alcohol. Drain off and dry slide over flame. Wipe back and edges of slide with piece of wet paper towel to remove excess stain.

CAUTION: If alcohol is left on too long or used to excess it will wash the blue stain out of the neutrophils and cause them to appear pink. They will not, however, show the relatively large deep red granules of the eosinophils.

5. Examine under the oil immersion lens.

It is not necessary to demonstrate an eosinophilia of 10 per cent as stated by Cohen and Rudolph (5). A definite increase over the usual 2 or 3 per cent, which is found in control smears, is sufficient evidence for eosinophilia. If an eosinophilia is demonstrated, regardless of other considerations, the burden of proof is upon the phy-

* The Hansel stain and stain racks may be obtained from most commercial houses supplying allergists or from the Tide Laboratories, Inc., 634 N. Grand Blvd., St. Louis 3, Mo.

sician who states that the condition is not allergic. The absence of eosinophils, however, does not rule out the RURI of allergic origin.

Occurring with almost identical frequency in children and often in association with the RURI, is a condition now termed "perennial allergic rhinitis" although the older terms, "chronic nasal catarrh" and "vasomotor rhinitis" are more familiar. This disorder, which will hereinafter be designated by initials "PAR," has also been termed "hyperfunctioning rhinitis" and "intumescent rhinitis." PAR is also an important allergic disease in adults and occurred in 35 per cent of a series of 200 successive patients referred for consultation (14).

The underlying pathology is a chronic, persistent allergic edema of the nasal mucous membranes. The disease may perhaps be a milder or chronic form of the RURI, which is characterized by intermittent edema. Most physicians do not differentiate PAR from the RURI although they are different clinical entities despite their close relationship, and if one of the terms employed above is not used, usually include both diseases under the term "chronic sinusitis." Just as in the case of the RURI, PAR has been sadly neglected by the pediatrician who in most cases is not aware of its allergic origin.

PAR is often very easily diagnosed by the history alone and by the same criteria which are recorded in Table XVII. Again, the mother will frequently state as the chief complaint, "My child has a cold all the time," or "I can't tell when he has a cold and when he doesn't," or "He never seems to be able to blow his nose." The chief symptoms, because of the nature of the underlying pathology, are sneezing or nasal discharge or obstruction or any combination of these. Occasionally the nasal obstruction leads to a chief complaint of mouth breathing. The symptoms may be perennial without seasonal variation although many individuals are worse during the so-called "house dust season" which starts when the weather begins to change in the fall and lasts until the heat is turned off when warm weather starts the following spring. In other children, however, PAR is complicated by "seasonal allergic rhinitis," i.e., the various forms of pollinosis as tree, grass (rose fever) and weed (hay fever). The symptoms of PAR are very similar to those of pollinosis though they are rarely as acute. The edema of the nasal mucous membranes in

both the RURI and PAR predisposes to secondary infection which occurs very frequently in the RURI.

The chronic nasal congestion associated with PAR often causes the child to sniff and snort, a state of affairs which becomes very annoying to the parents who insist that "if only he would blow his nose properly he would not have to make those noises." This, of course, is not true because no matter how hard the child blows his nose, he cannot blow out the congested mucous membranes which are causing the trouble, though the effort may occasionally cause epistaxis. The post-nasal drip which may occur as a result of PAR may also induce the annoying habit of constantly "clearing the throat" or "hawking," in popular parlance. Much more serious is the development of a chronic, intractable cough, usually worse at night, as a result of a post-nasal drip, or, more rarely, a persistent laryngitis. It is also occasionally observed in PAR that when the patient lies on one side, the dependent side of the nose will be obstructed by congestion while the upper will clear. On changing position the obstruction will be reversed. This may lead to the child's constantly changing his position while in bed, the restlessness resulting in loss of sleep.

Bowen and Balyeat (1) have described certain mannerisms (illustrated in Figure 41) very characteristic of the child with nasal allergy. These are "nose wrinkling" (also called "bunny nose" or "rabbit nose") and "mouth wrinkling" which are due to an attempt to relieve itching of the nose due to nasal allergy. Another mannerism has been very aptly termed by Bowen* the "allergic salute." This is done by the child's elevating the tip of the nose with the palm of the hand in an upward movement. It is altogether different from the common gesture used by the child to wipe off mucus from the nose. The child gives the "allergic salute" or "Bowen's salute," as it is sometimes termed, because he has discovered by experience that this movement will somewhat relieve the nasal obstruction. The mechanism appears to be that the child with nasal allergy often has a watery secretion which spreads in a film from turbinate to septum. Pressure inward and upward on the tip of the nose tends to widen the in-

* This was first reported by Bowen at a meeting in Memphis, Tenn., in 1928. Personal communication.



FIG. 41. Reproduced with the kind permission of Dr. Ralph Bowen. (a) and (b) illustrate Bowen's "allergic salute." (c) and (d) illustrate respectively "nose wrinkling" and "mouth wrinkling."

transnasal space, separating the turbinates from the septum which breaks the film and promotes nasal aeration.

The RURI is, at any age, a not infrequent precursor of bronchial asthma; curiously this appears to be less true with PAR. Since both are basically due to edema of the nasal mucous membranes just as asthma is due for the most part to edema of the mucous membranes of the bronchi, these conditions might well be termed, for the purposes of illustrating their significance to the patient, "asthma of the nose."

The complications of the RURI are essentially the same as those of any acute upper respiratory infection. Common complications

of PAR in the adult are sinusitis, nasal polyposis and anosmia. The latter two, fortunately, are rare in children although perhaps children have anosmia but do not complain about it. PAR in both the adult and the child may result in sinus infections because of edema of the membranes with defective drainage, usually ethmoiditis in the child. Hearing difficulty may occur in both the child and the adult due to chronic edema of the eustachian tubes but, fortunately, this is not as frequent as might be expected.

One would expect almost *à priori* that long continued nasal obstruction of allergic origin would result in maldevelopment of the face. It has been stated that failure of development of the sinuses, principally the maxillary and ethmoids (because the frontal sinuses are undeveloped in the young child) gives rise to the so-called "allergic facies." Cohen (4) commented upon the frequency in allergic children of dental abnormalities associated with malformations and disturbances in growth of the dental arches and attributed this to interference by the allergic condition with the development of the facial bones. Straub (19) in a study of 144 children under orthodontic treatment found that about 40 per cent suffered from chronic nasal allergy and in seven instances (17 per cent of cases) allergic gingivitis was also diagnosed. Straub agrees with those who urge the early diagnosis and treatment of nasal allergic conditions as an important method of reducing the incidence of dentofacial anomalies. Miller (15) in a more recent study, however, stated that he could find no evidence that allergy of upper respiratory tract had any bearing on the production of dental arch deformities or occlusal relationships. This subject, apparently, needs further clarification, particularly because of other factors than allergy or infection which may influence sinus growth as discussed by Rosenberger (18).

The specific treatment of the RURI and PAR is exactly the same as for bronchial asthma. In the case of the RURI this is highly successful. PAR, on the contrary, is second among the allergic diseases only to the chronic urticaria of adults in the difficulty of obtaining satisfactory relief. Hypersensitivity to house dust, often clinically and nearly always by skin test, is usually present in both, but more commonly in PAR, and hyposensitization to house dust and other inhalants is commonly necessary. In young infants and children foods, especially cow's milk, are commonly important factors. Treat-

ment with bacterial vaccine is often employed, sometimes apparently with good results. Tonsils and adenoids, if diseased, must be removed, and polyps and sinusitis of infectious origin as well as other organic disease of the nose and throat treated as indicated. It must be emphasized that none except emergency operative procedures should be carried out on the nose and throat during the seasons of grass and weed pollination because of the marked tendency of these individuals to develop pollen asthma. In very rare instances hypothyroidism may result in myxedema of the nasal mucous membranes with or without other evidence of hypothyroidism and produce the symptoms of PAR. I have studied one such case in a child and seen two adults in consultation with this disorder.

The symptomatic prophylactic treatment of the RURI will often produce highly satisfactory results *if properly carried out*. It is possible in most instances to abort the attack and in those instances where the RURI is followed by asthma, to prevent or minimize the asthmatic attack. This is one of the most highly gratifying procedures in the armamentarium of the pediatric allergist. The routine to be followed is exactly the same as that previously described for the prevention of asthmatic attacks following upper respiratory infections as discussed in Chapter 36.

The symptomatic relief of PAR is a much more difficult matter. The antihistamines will often relieve sneezing and nasal discharge but rarely nasal congestion. Nose drops rather than nasal sprays offer the best symptomatic relief. I commonly prescribe a nose drop containing ephedrine 1½ per cent or neosynephrine ¼ per cent to be used on arising and before lunch and supper. At bedtime Privine nose drops (Ciba) 0.05 per cent may be used and also repeated once during the night if necessary. The patients are always cautioned never to use the Privine nose drops more than twice in twenty-four hours and I have never observed sensitivity or nasal damage as a result of the use of Privine nose drops in this manner. The use of cortisone nose drops has been uniformly unsuccessful. It may well be that hydrocortisone nose drops or sprays will be developed which will prove exceedingly helpful. I have on rare occasions used oral cortisone in adults seen in consultation who could not be otherwise relieved, but have not yet used the steroids in children for this purpose.

Occasionally when the nose is so completely obstructed by congestion that the drops will not penetrate, a hot bath will open the nasal passages sufficiently for this purpose.

I am not convinced that the addition of an antihistamine to such nose drops increases their effectiveness and this may make the drops more irritating.

In summary, it may be stated that the frequently recurring or "continuous" cold of childhood is nearly always due to allergic nasal mucous membranes. These children may be divided into two groups. In one group the symptoms are for the most part intermittent and acute, and resemble the common cold. This should be designated the recurrent upper respiratory disorder or infection of allergic origin (RURI). The second group of children suffers less acutely as a rule but more continuously from chronic allergic edema of the nasal mucous membranes and this condition is presently termed "perennial allergic rhinitis" (PAR) in contrast to seasonal allergic rhinitis or pollinosis although both conditions may coexist in the same individual. The diagnosis is made chiefly by the history and the appearance of the nasal mucous membranes and confirmed by the finding of an eosinophilia in the nasal smear. Both the RURI and PAR should be thoroughly studied from the standpoint of allergy. House dust is one of the more important allergens in this disease. Both conditions can be treated quite satisfactorily from the symptomatic standpoint by antihistamines, nose drops and cough medication. Occasionally an antibiotic is desirable if the problem of superimposed infection is involved. From the standpoint of specific therapy the RURI responds very nicely but PAR often responds only with great difficulty. It is important to study and treat these diseases not only for the purpose of alleviating the distress which they cause but particularly as prophylactic measures for bronchial asthma which may follow both, especially the RURI.

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VARIOUS FORMS OF URTICARIA, ANGIO- EDEMA, ERYTHEMA MULTIFORME AND ERYTHEMA NODOSUM

URTICARIA AND ANGIOEDEMA

THESE DISEASES occur with a fair degree of frequency in infancy and childhood. In the series of 516 children reported by MacKinney and Glaser (8) the incidence was about 16 per cent as compared with 12 per cent in the 100 children reported by Clein (5) and 10 per cent in the 250 children reported by Ratner and associates (9). These figures correspond reasonably closely and indicate an average incidence of urticaria as a symptom requiring the attention of the allergist in about 14 per cent of children. It must be remembered, however, that all three practices are heavily loaded with allergic children and this essentially represents the incidence of the occurrence of urticaria in such children. In the 200 adults studied by MacKinney and Glaser (8) for the sake of comparison, urticaria occurred in 35 per cent of cases or well over twice as often as in pediatric practice. It is also exceedingly uncommon for urticaria in children to last as long or be as troublesome as it often is in adults.

Urticaria in childhood is most commonly due to some particular food, especially strawberries, nuts, and egg. Occasionally a child's face will erupt with urticaria during severe crying. This is a vasomotor reaction which has no relationship to allergy. Foci of infection are rarely found as etiological factors in children. Urticaria may also be caused by reactions to drugs and sera and occasionally, in exquisitely sensitive children, to trans-epidermal penetration on contact with substances such as egg and silk, for example. Siegel and Bergeron (11) in a study of urticaria and angiodema in a series of 115 children and young adults found that the etiological factor in almost one-quarter of the cases was the injection of penicillin; the cause could not be determined in about one-third of the patients.

Their cases were also studied with special reference to the electrocardiogram. Significant changes were found in only two of ninety-eight patients and these were apparently due to causes other than the urticaria and/or the angioedema.

Physical agents, such as heat, light and cold may also on infrequent occasions produce urticaria. Urticaria to inhalant substances also occurs (see Chapter 42 on urticaria due to pollen), but is apparently very infrequent in children. Derbes and Engelhardt (7) described a boy of eleven years who, when exposed to the odor of fresh paint, would develop asthma and urticaria.

Urticaria secondary to an acute infection is of fairly frequent occurrence. Connor and Milzer (6) reported urticaria in patients convalescing from scarlet fever who gave positive skin reactions following the intradermal injection of suspensions of hemolytic streptococci which had been isolated from their throats. Negative reactions were obtained following Berkfeld filtrates of these bacteria or injections of Dick toxin or human convalescent serum. This suggested to the authors that bacterial allergy might be a factor in certain complications of scarlet fever such as hemorrhagic nephritis or non-suppurative arthritis. Bivings (4) in 1946 reported twenty-two cases of acute infectious urticaria in children. A history of allergy was negative in eighteen of these patients. The common focus of infection was the throat, next otitis and then pyelitis. There were no organisms common to all cases. I have seen urticaria occurring in several children following smallpox vaccination and have the impression that this also is a form of acute infectious urticaria.

Berger (3) described the occurrence of urticaria in an eighteen-month-old child following the intramuscular injection of blood from an adult who was sensitive to horse serum. The child had previously been treated with antistreptococcic and normal horse serum. Bass (1), in 1941, reported a girl who developed hives on contact with ammoniated mercury and also on contact with metallic mercury. Bass (2) subsequently noted that this girl developed angioedema and urticaria about the lips, mouth and cheeks from bits of amalgam on the dentist's fingers in filling one of her teeth. The filling itself was left in place without ill effects. However, in another fourteen-year-old girl who was exquisitely sensitive to mercury, it was necessary to remove the amalgam filling for the relief of generalized urticaria

and angioedema. A passive transfer test was performed with this girl's blood serum and when a small amount of ammoniated mercury ointment was applied to the prepared site, a definite red wheal appeared. The control test on the opposite arm was completely negative. A ten-year-old boy who developed urticaria from metallic mercury was also described.

TREATMENT OF URTICARIA

The best treatment is to remove the cause, if this can be discovered. Skin tests are very rarely helpful. If a food is suspected, an elimination diet should be tried. In chronic cases, foci of infection must be eliminated although this is rarely the cause in children.

For symptomatic relief, the antihistaminics are commonly very helpful. Occasionally some relief is obtained with ephedrine sulphate, 25 mg. or 50 mg. every four hours. When these drugs fail, the injection of epinephrine 1/1000 may help. Roberts (10) reported a series of ten children ranging in age from two and one-half to six years relieved by benzidrene sulfate in starting doses of 2.5 mg. every three or four hours. In two instances, it was necessary to give 5 mg. every four hours. Everything else failing, ACTH or cortisone commonly gives very satisfactory relief. Fortunately, at least in children and for the most part in adults, the disease is self-limited.

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PAPULAR URTICARIA

(Lichen Urticatus; Urticaria Papuloso)

According to Shaffer and associates (2) this disease affects children predominantly, especially between the ages of two and seven years. It is rare in early infancy and in later childhood. In temperate climates, it is seen with greatest frequency in the hot weather months, reaching its greatest peak in mid-summer and only rarely occurring in the winter. The eruption tends to be distributed on the exposed portions of the skin, particularly of the extremities, head, neck, and shoulders. The genitalia, buttocks, webs of the fingers and intertriginous sites are usually exempt, which is of great help in the differentiation of this disease from scabies. The basic individual lesions are discrete wheals and papules with all grades of transition between those two types. The wheals are usually few in number and may be absent. The papules are numerous and persistent and appear at times to develop from the wheals, and are the characteristic lesions of the disease, without which the diagnosis cannot be made. After recurring for a number of hot weather seasons the disease commonly disappears spontaneously.

Rook and Frain-Bell (1) have thoroughly reviewed literature of the subject of papular urticaria with particular reference to children and reported on a series of 100 patients studied by them. They pointed out that as long ago as 1879 Jonathan Hutchinson suggested that many cases were due to insect bites. In the series of Rook and Frain-Bell the sexes were about equally divided. The patients ranged in age from two weeks to seven years with an average age of one year and ten months; about 90 per cent were under three years of age. Most of the cases occurred during the summer and the legs and lower trunk were chiefly involved. It was found in 85 cases where special inquiry was made that in about a third of these another

member of the family was affected. After reviewing previously suggested causes of papular urticaria, such as allergy to foods, psychosomatic factors and infection, Rook and Frain-Bell concluded that while the possibility that papular urticaria is a syndrome of multiple etiology cannot be completely excluded, there was no evidence of any other cause than insects in their own cases, and no convincing evidence in the literature that any other cause has ever been reliably established.

Before the acceptance of the concept of insect etiology, papular urticaria was generally highly resistant to treatment. However, since it has been known that most cases are due to insect bites, therapy in that direction has been quite satisfactory. Shaffer and associates (2) recommended the following treatment:

1. A spray of 5 per cent DDT in Flit* is to be used daily in the household. Baseboards, the cellar, the bed frames and upholstered furniture should receive special attention.

2. A powder of 5 per cent DDT should be dusted on dogs and cats and under cushions and rugs and wherever the spray cannot be used.

3. Contact with dogs and cats should be avoided.

4. All collections of sand should be removed.

5. The child should be dusted lightly and daily with a special powder (5 per cent DDT in talc) which should also be dusted on his bed clothes and mattress.

The majority of patients so treated develop no new lesions and the itching disappears within two weeks.

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URTICARIA FACTITIA

In this disease the skin shows very marked dermatographia. Severe cases are uncommon in infancy and childhood. The cause is

* A pyrethrum containing insecticide manufactured by the Esso Standard Oil Corporation, Linden, N.J.

unknown although the disease may be an expression of physical allergy or a non-allergic reaction to toxemia and perhaps sometimes from foci of infection. It is mentioned here because these patients are not infrequently referred to the allergist for a study. The dermographism is occasionally accompanied by very severe pruritis. Some symptomatic relief is afforded by antihistamines. Duke (1) states that patients, whose skin is so irritable that they are made miserable by itching resulting from rubbing by rough garments or slight scratches, may be rendered relatively tolerant by frequent mechanical irritation of the skin, generally with a stiff brush. Although itching and redness may be relieved, wheals continue to appear under the influence of scratches. The only problem I have ever had with this disease in pediatric practice was a boy five years of age who also had badly diseased tonsils. Following their removal, the acute condition gradually subsided over a period of several months, although he had a marked dermatographia which did not cause subjective symptoms when last seen at the age of nine years.

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URTICARIA PIGMENTOSA

This disease, also, is not of allergic origin but is discussed here because children suffering from this are occasionally referred to the allergist for study. It is not particularly common. Lipschutz and Shaffer (1) who reported a case in a newborn infant in 1951, stated that only about 400 cases had been noted since the disease was first described by Nettleship in 1869. However, many cases have been seen which have not been reported, at least four in my own personal experience, and it is encountered sooner or later by almost every pediatrician. It commonly starts during the first year of life, beginning with wheals which usually disappear after several weeks, leaving yellow or brownish yellow macules about 0.5 to 1.5 cm. in diameter, usually limited to the trunk. Characteristically, a macule when rubbed becomes a wheal. The lesions are nevoid, rarely nodular or bullous, and tend to disappear at puberty. There is at present no satisfactory treatment.

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ERYTHEMA MULTIFORME

This disease Becker and Obermayer (1) describe as a clinical rather than an etiologic entity and reference is made to their work for a detailed discussion of its manifestations. As briefly defined by Foerster (3), it is an acute, inflammatory disease, often attended by systemic disturbances, and characterized by an eruption of red or bluish-red macules, papules and tubercles, or vesicles and bullae, one type of lesion usually predominating. It is often bilateral and symmetrical in distribution with marked predilection for the face, neck and dorsal surfaces of the extremities below the knees and elbows. It usually runs its course in two or three weeks and occasionally recurs through a period of years, commonly in the spring or autumn. Schwartz and Brainerd (4) discussed this disease with special reference to its occurrence in children as a complication of smallpox vaccination. They state that, while at times the syndrome may appear spontaneously without any associated illness, it has been noted that it may be in some instances associated with sulfonamide sensitivity, horse serum sensitivity, Vincent's infections, and rheumatic fever. Erythema multiforme may occur as a reaction to other drugs and infections and Waite (7) reported a case associated with bacillary dysentery. I have seen the disease occur as a reaction to penicillin and in one instance complicating ulcerative colitis in a child, the severity of the skin manifestations paralleling the severity of the colitis. The disease is believed to be due to an allergic reaction and a history of allergy is said to be obtainable in 50 per cent of the cases (4).

When erythema multiforme involves the mucous membranes, it is termed the Stevens-Johnson syndrome (6). All orificial mucous membranes may be involved and this has been termed by Costello (2) "erythema bullosum malignans—pluriorificial type." Under such conditions, the illness is often very serious. If the conjunctivae are involved, blindness may result. Such a complication was described by Shaffer and Morris (5) as a reaction to tridione. Their paper contains a good bibliography of this condition.

No satisfactory treatment for this disease was at hand until the

development of ACTH and cortisone, which I have used satisfactorily in the treatment of a case complicating rheumatic fever in a child. Weeks and Lehmann (8) have since reported similar success with these drugs.

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ERYTHEMA NODOSUM

Erythema nodosum may be defined as an erythematous cutaneous eruption manifested by the occurrence of deep, discrete, subcutaneous nodules usually limited to the extremities (3).

The monograph of Doxiadis (1), published in 1951, reviews in detail the salient features of this condition and it is from his report that the material for this discussion has been largely obtained. The disease was first described by Underwood in 1795, and the present name was given to it by Willan in 1808. The principal feature of erythema nodosum is a rash which, at the onset, is usually accompanied by fever, localized pains and malaise. The typical lesion at the onset is a shining, bright red swelling of an irregular round or oval shape, varying in size from 1 to 5 cm. in diameter. It is indurated and tender on palpation. Two or three or more lesions may coalesce in the first few days of the eruption to form a large erythematous area. The extensive redness begins to subside within twenty-four hours of attaining its greatest intensity and individual lesions can then be easily distinguished. Within one to three days

the red areas become stabilized, the lesions lose their shiny appearance, become less raised and the tenderness subsides. The bright red color changes within four to ten days to dark red and then to purple and blue. Finally the lesion fades, acquiring in the last stages a brownish tinge which may be visible up to two weeks after the complete disappearance of the blue color. A nodule which appears in the first few days beneath the lesion can commonly be felt up to two weeks after the disappearance of the blue color. The sedimentation rate is markedly elevated. Recurrences take place in about 4 per cent of cases.

The disease is uncommon in the first two years of life but does occur; the youngest reported case occurred at about the age of seven months following sulfathiazole. In males most cases occur below the age of fifteen years and in females between fifteen and twenty-five years. Females tend to predominate, especially after puberty.

Doxiadis, whose personal experience was largely in Europe, and extended over a twenty-year-period, believes that this condition is a non-specific syndrome always occurring during the active stage of various infections, which differs in relative importance from country to country. In Europe, and perhaps South America, the commonest associated infection is tuberculosis, with infections due to the B-hemolytic streptococcus taking second place. In North America infections with the B-hemolytic streptococcus appear to be more often the cause of erythema nodosum than tuberculosis. Finally, in small areas of the United States, coccidiomycosis is a common etiological factor. When the disease is associated with a reaction to a drug, it is most commonly sulfapyridine. This and the other sulfonamides are not the causative agents but act as provocative factors for the eruption of erythema nodosum only in the presence of an infection commonly associated with it.

Of particular interest to physicians of the United States is the study of McIntosh (2) who reviewed the cases at Babies Hospital in New York over a sixteen-year-period. During that time erythema nodosum was observed in forty-three children less than thirteen years of age, a case incidence of approximately one in 1200 (about 0.084 per cent). Half were between seven and ten years of age. Three were seen in infants, one and one-half to two years of age. The sexes were about evenly divided. Most cases occurred

in February. In only five instances had there been previous attacks. The family history for allergy was not in excess of that found in random samples of the hospital population. A previous history of allergic diseases in the patient himself was rarely elicited. About half had had sore throats prior to the eruption. The associated diseases which could be clearly identified were surprisingly few. In only four instances could primary tuberculous infection be established with reasonable certainty. There was one unquestionable case of rheumatic fever and two questionable cases. Many patients exhibited skin sensitivity to B-hemolytic streptococcus test material and also an increased sedimentation rate without manifesting any of the clinical phenomena of rheumatic fever. A minority of the total group had positive tuberculin tests. The hypothesis is advanced, admittedly on the basis of a limited experience with erythema nodosum, that when it is causally related to tuberculosis, it is associated with the efflorescence of the primary infection. Cases, on the other hand, which appear months after the initial tuberculosis infection, or second attacks developing in tuberculin positive children, are thought to represent the expression of hypersensitivity to some other allergen, often a B-hemolytic streptococcus. In any given case before one accepts the relationship of the infection to tuberculosis on the basis of the positive tuberculin test alone, it is desirable that a search be made for hypersensitivity to other allergens. The frequency of occurrence of erythema nodosum among the inhabitants of Scandinavian countries does not lead to its more frequent appearance in American descendants of Scandinavian stock, as one might expect of susceptibility genetically transmitted as a constitutional trait.

No specific treatment is available or necessary for the disease since it is self-limited. Salicylates are useful. Cortisone and ACTH may be used if not contraindicated by the presence of active tuberculosis (3). I have seen good symptomatic relief in two cases from these drugs.

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ALLERGY TO DRUGS

THE LITERATURE appears to offer no universally accepted, satisfactory, practical definitions of various types of abnormal reactions to drugs. It was therefore necessary for Berkowitz, Glaser, and Johnstone (2), in order to carry out properly a study on the incidence of drug allergy in children, to formulate definitions which would clarify this subject, at least insofar as the purpose of their study was concerned. These authors, therefore, stated as follows:

"By drug idiosyncrasy is meant an abnormal *quantitative* response to a drug. For example, a small therapeutic dose of atropine as used to control sneezing in pollinosis may cause slight dryness of the nose and throat—its normal physiological reaction. If such a dose causes a generalized erythema, dilatation of the pupils and abdominal distention, this represents an abnormal quantitative reaction to the drug in the direction of its expected effect when administered in toxic doses. Another patient might conceivably be given, through error, a truly toxic dose of atropine and demonstrate only minimal physiologic reactions. This would represent idiosyncrasy in the direction of a decreased quantitative response to the drug.

"By drug 'allergy' is meant an abnormal *qualitative* response which has no relationship to the normal physiological reactions of the drug in any dosage, as for example, urticaria produced by penicillin. The term 'hypersensitivity' when applied to a drug usually denotes 'idiosyncrasy' as described above in the direction of an increased response to the physiological action of the drug.

"Confusion arises because the terms 'hypersensitivity' and 'allergy' are so frequently used interchangeably. If one makes the statement that August-to-frost pollinosis is due to allergy to ragweed pollen or that it is due to hypersensitivity to ragweed pollen, there is no confusion as to what is meant. However, in speaking of drugs, one must be more precise and the definitions given above are

at least appropriate to this discussion. It is possible that drug idiosyncrasy may be in some way related to drug allergy since, in a sense, it represents a state of altered reactivity, but just what this relationship may be is at present unknown."

In their study it was attempted to differentiate between the better known typical allergic reactions to drugs such as rashes of various types, angioedema, asthma, rhinitis and pruritus and what were grouped as "side reactions," because there could be some question as to whether or not these represented true allergic responses to the drugs. In a young child, for example, nausea and vomiting following a drug may be merely an expression of the patient's resentment toward being compelled to take any type of medication. Other apparent "side reactions" may be due to infection and not to the drug administered. These included ataxia, abdominal distress, bladder discomfort, depression, diarrhea, dizziness, drowsiness, excitement, fever, headache, hematuria, irritability, joint pains, stomatitis, and others.

These so-called "side reactions," however, occurred so much more commonly in the allergic than in the non-allergic child that in most instances they probably represent true allergic reactions. The term, "minor drug allergies" might, therefore, have been better used than the term "side reactions." Special attention was given to the relative incidence of drug intolerance in the allergic as compared with the non-allergic child. This study included 500 children of whom 332 (66.4 per cent) were considered allergic and 168 children (33.6 per cent), who had no history of allergic disease, were considered non-allergic.

Table XVIII shows the frequency of usage of the twenty most commonly employed drugs in pediatric practice in Rochester, New York at the time this study was made. It is an interesting commentary on present day methods of treatment, concerning which time will give the ultimate judgment, that penicillin is used almost as frequently as aspirin and these are the two drugs most commonly employed in pediatric practice.

Table XIX records the incidence of drug reactions, both allergic and those grouped as "side reactions." Twenty per cent of the allergic group gave allergic reactions to drugs as compared with

TABLE XVIII

DRUGS MOST COMMONLY USED	No. of Patients
1. Aspirin.....	450
2. Penicillin.....	411
3. Sulfonamides.....	292
4. Phenobarbital.....	260
5. Codeine.....	231
6. Aureomycin.....	208
7. Pyribenzamine.....	188
8. Ephedrine.....	141
9. Benadryl.....	140
10. Terramycin.....	112
11. Other antihistaminics.....	77
12. Aminophyllin.....	80
13. Epinephrine.....	75
14. Other sympathomimetics.....	80
15. Opiates other than codeine.....	68
16. Atropine.....	65
17. Sedatives other than phenobarbital.....	57
18. Chloromycetin.....	45
19. Iodine.....	32
20. Streptomycin.....	20

TABLE XIX

PERCENTAGE INCIDENCE OF ALLERGIC AND "SIDE EFFECTS" TO
DRUGS IN ALLERGIC AND NON-ALLERGIC CHILDREN

	Incidence of Allergic Reactions			Incidence of "Side-Reactions"		
	In Allergic Children	In Non-allergic Children	Overall Incidence	In Allergic Children	In Non-allergic Children	Overall Incidence
Penicillin	10.0	—	6.8	2.1	—	1.4
Sulfonamides	6.7	4.7	6.1	7.7	2.3	6.2
Aureomycin	3.7	—	3.3	17.2	—	14.0
Terramycin	3.4	—	2.6	10.2	8.3	9.8
Benadryl	2.2	—	2.1	11.3	—	10.7
Atropin	2.0	—	1.5	8.3	—	6.2
Aspirin	1.9	—	1.3	2.3	0.7	1.7
Pyribenzamine	1.7	—	1.6	14.2	—	13.3
Codeine	1.5	—	1.3	3.6	—	3.0
Phenobarbital	—	—	—	13.0	1.5	9.6
Ephedrine	—	—	—	7.3	—	6.3
Aminophyllin	—	—	—	11.5	—	11.2
Epinephrine	—	—	—	3.0	—	2.6
Totals	20.0	2.4	12.8	36.0	3.5	25.0

2.4 per cent of the non-allergic group. "Side reactions," better termed "minor drug allergies," occurred in 36 per cent of allergic children as compared with 3.5 per cent in the non-allergic children. Thus over half (56 per cent) of allergic children may be expected to give some type of a disagreeable reaction to drugs, if the "side reactions" or minor drug allergies are included, as compared with about 6 per cent of non-allergic children.

Aspirin, the drug most commonly used in pediatric practice, was taken by 450 children of whom 306 were allergic. Six (1.9 per cent) developed allergic reactions to this drug. No allergic reactions occurred in the 144 non-allergic children. The allergic reactions to aspirin consisted of urticaria in two children, asthma in two children, angioedema in one child and a morbilliform eruption in one child. Eight children (2.3 per cent) developed drowsiness or abdominal discomfort from aspirin. These were classified as "side reactions."

Codeine was given to 231 children, of whom 191 were allergic. Three of the allergic individuals (1.5 per cent) developed allergic reactions, two urticaria and one a generalized morbilliform rash. "Side reactions" such as nausea, vomiting, restlessness, gastric distress, and excitement occurred in seven (3.6 per cent) of the allergic group; no reactions occurred in the forty non-allergic children.

Phenobarbital was used by 260 of the children, of whom 183 were allergic. There were no allergic reactions to this drug. However, twenty-four (13.1 per cent) showed "side reactions." Twenty were excited by this ordinarily sedative drug, two had emesis, one nausea, and one a prolonged "hangover." Only one non-allergic individual had a "side reaction" and this was excitement.

The above observations suggest very strongly that if codeine and/or phenobarbital disagree with a child, that child is very likely an allergic individual.

Atropine was administered to sixty-five children, of whom forty-nine were allergic. One allergic child (2.0 per cent) developed a generalized rash. "Side reactions" such as abdominal pain, flushing or erythema occurred in four (8.3 per cent) of the allergic group.

With respect to the other drugs in this study, except for penicillin, which will be discussed subsequently, reference is made to the original publication (2). A complete discussion of the general subject of

drug allergy has been published by E. A. Brown (3) who, also, in another publication, (4) has listed the types of reactions which may occur from a great variety of drugs.

It should be mentioned that in attributing an allergic reaction to any particular drug, an occasional unsuspected error is the possibility that the reaction may be due to the excipient used in its preparation. At one time a leading pharmaceutical house prepared a series of drugs using as excipients substances of no or minimal allergenicity. The demand for this product, however, was so slight that its manufacture was discontinued. It is also true that occasionally urticaria and or angioedema may occur as a reaction to the infection being treated, in the case of such disorders, rather than to the drug being employed to treat the infection. This is discussed in Chapter 44.

PENICILLIN

This drug, because of its great clinical importance is of particular interest from the standpoint of allergy. In the study of Berkowitz and associates (2) it was administered to 411 children of whom 280 were known to be allergic. The route of administration was not recorded. It is, of course, now generally realized that severe reactions are much less likely to occur when the drug is given orally than parenterally. Of the allergic children who received this drug, 10 per cent developed reactions. No allergic reactions occurred in the non-allergic children. The overall incidence of an allergic response to penicillin was 6.8 per cent. The allergic reactions encountered were: urticaria or angioedema in fourteen children, morbilliform eruptions in eleven, and atopic dermatitis in two. Classified as "side reactions" were vomiting, diarrhea and joint pains, each of which occurred in one child, and local swelling and pruritus at the site of injection in another child. These could well have been allergic reactions as they occurred only in allergic children. These figures compare not too unfavorably with the series of Collins-Williams and Vincent (5), in which the total reactions which might have been due to penicillin was 8 per cent of eighty-five allergic children and 2 per cent in 515 non-allergic children. Their article tabulates in detail all of the various types of untoward reactions which may occur following the administration of penicillin.

Fatal reactions to the injection of penicillin appear to be very definitely on the increase, as indicated by the report and warning of Rosenthal (11). Although these appear to occur much more frequently in adults than in children, it is my practice never to give an injection of penicillin unless the parenteral procedure is indicated by the urgency of the situation. I prefer to give the penicillin orally and, unless there is a contraindication, to use some other antibiotic which may be expected to be equally effective, saving the penicillin, which is still the most important antibiotic, for some more urgent occasion.

Thus far I have been able to find reports of but three deaths from penicillin in the pediatric age group. Nelson and Braslow (10) reported a death in a three and one-half-month-old Mexican girl, apparently as the result of a Schwartzman reaction; Harpman (7) in a three and one-half-year-old child who became dyspneic and unconscious one hour after an injection of penicillin and died two and one-half hours later, and the case of Rosenthal (11) was an eighteen-month-old girl who developed respiratory distress and died a few minutes after the injection. In all three cases procaine penicillin had been used, and necropsies were made. In the patient of Nelson and Braslow there was congestion of the brain and viscera with mild meningitis and gangrenous ulcers of the buttocks and legs; in Harpman's patient there were a few petechial hemorrhages on the surface of the lungs and brain and gross pulmonary emphysema. In Rosenthal's case there was gross congestion of all viscera.

It is well known that disagreeable reactions to penicillin may occur in patients who have never been previously treated with penicillin. The possible mechanisms by which previous exposure with resulting sensitivity may have occurred have been detailed by Goltman (6). The more significant of these are as follows: (1) transfer and sensitization in utero, since penicillin passes the placental barrier and may be found in the fetal blood in two-thirds of the concentration of the maternal blood; (2) common antigen effect due to biogenetic relationship with other types of fungi or their products; (3) inhalant antigen effect, since penicillin mold is a common contaminant of the environment; (4) ingestion presensitization, for example, by Roquefort and other cheeses ripened by *Penicillium* of various

species, and (5) those rare cases of penicilliosis in which an individual has been infected by a *Penicillium* fungus.

Some authors, as Collins-Williams and Vincent (5) feel that skin testing with penicillin has little value but Matheson (9), whose experience is considerable, believes that it is a worthwhile procedure. He stated that although the skin test with penicillin in the more frequent delayed or serum sickness-like type of penicillin reaction is uniformly negative, it is frequently positive in the immediate constitutional type of reaction to this drug. Although such a reaction is infrequent, its serious consequences when it does occur become a distinct hazard in therapy with this antibiotic. It is Matheson's opinion that patients who give this type of reaction may be screened out in advance by proper skin testing with penicillin.

TECHNIC (Matheson)

For the scratch test, 1 drop of freshly prepared solution of aqueous crystalline penicillin G containing 5000 units of penicillin per cc. is used. If a negative skin test results, one may proceed with an intradermal test using 0.02 to 0.05 cc. of an aqueous crystalline penicillin G solution containing 1000 units of penicillin per cc. Weaker solutions than the above-described should be used where there is a history of a clinical reaction, especially of the immediate or accelerated type, resulting from previous penicillin contact. For the control test, the diluent used for the preparation of the penicillin solution is employed.

SIGNIFICANCE OF THE SKIN TEST

1. An immediate positive skin test with penicillin in a child who has previously been treated with penicillin is highly suggestive of the presence of a high degree of potential clinical sensitization. The injection of penicillin into such a child will probably be followed by a constitutional reaction.

2. A negative skin test with penicillin does not rule out the presence of potential clinical sensitization.

3. A constitutional reaction, even if mild, resulting from a skin test with penicillin indicates the existence of a high degree of clinical

sensitivity and is an absolute contraindication to the use of penicillin therapy.

While hyposensitization has been reported to have been carried out successfully in a few patients sensitive to penicillin (1) this will not become a generally accepted procedure unless more information indicating its practicality becomes available. The whole problem of preventing reactions to penicillin is best summed up in the words of Kern and Wimberly (8) who stated that "the best way to prevent a penicillin reaction in a potentially or proven sensitive patient is to give another drug."

The treatment of the fulminating penicillin reaction is the same as that of any other severe anaphylactic reaction. An injection of epinephrine should be given immediately, steroid therapy started and other supportive measures used as indicated.

The studies of Berkowitz and associates (2), as previously discussed, indicate a very definitely higher (eightfold) incidence of drug reactions in allergic as compared with non-allergic children. For this reason, caution and close observation are indicated whenever any drug is given to an allergic child. It must be borne in mind that *the administration of any new drug to an allergic child is always an experiment*, and in most instances the new drug should be tried cautiously, at first, and in small amount, until the response of the child has been determined.

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INSULIN

The subject of allergy to insulin has been reviewed in detail by Vaughn and Black (6). The incidence of generalized reactions in diabetes mellitus appears to be about 1 in 1000 (6) or 1 in 1500 (5) cases. Siegal and Hertzstein (4) concluded that no special relationship exists between the presence of allergy in the diabetic and allergic reactions to insulin. In some instances the allergy appears to be related to the source of the insulin as, for example, when an individual can tolerate the drug prepared from the pancreas of a pig but not of beef. In such cases this is not true allergy to an endocrine product but to some impurity in the preparation.

Allergy to pure crystalline insulin does, however, occur. For the management of this condition Dolger (1, 2) suggested either rapid desensitization to insulin or the denaturization of regular or crystalline insulin by immersing the vial in boiling water for 15 minutes. This appears to be associated with some loss of potency of the insulin, about 10 to 20 per cent, but it may then often be used without allergic reactions. Nichols (3) has reported such a case in an eleven-year-old girl.

It would seem that the use of corticotropin or the adrenal corticosteroids might prove helpful in some instances.

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ALLERGY TO VACCINES

DEATH FOLLOWING VACCINE INJECTION

DEATHS related to the injection of vaccine in man are, according to Werne and Garrow (6), fortunately few. These authors reviewed the literature on the subject and reported two cases of their own of extreme interest and importance.

They described identical male twins, ten months of age, who died after the second injection of combined diphtheria toxoid and pertussis antigen, alum precipitated. The first injection had been given routinely a month previously from another ampoule of the same product. At this time one infant remained symptom free; the other vomited, cried considerably and had a fever of 38.3°C. (101°F.), but all symptoms subsided uneventfully within a few hours. At the time of the second injection at the age of ten months, no immediate ill effects were noted except that one twin bled slightly from the site of the injection. However, shortly afterwards, both infants vomited, consumed excessive amounts of water and then "fell asleep," and when next noticed by the parents, appeared "lifeless." They did not move in bed and could be aroused only by loud noises. One infant had a "staring expression," a temperature of 37.7°C. (99°F.), and when his diaper was changed, was found to be "ice cold" and "wringing wet" with perspiration. Early the following morning, sixteen hours after the injection, one infant was found dead; the other was gravely ill and died four hours later despite heroic efforts at therapy. Complete autopsies were done. Widespread lesions were encountered with vascular injury as the underlying cause. These findings are consistent with death from anaphylactic shock. Post-mortem passive transfer tests with the serum of the dead infants and the biological product were negative.

Examination of the preparation, which was the product of a very reliable manufacturer, showed sterility and no abnormality, such as, for example, excessive free diphtheria toxin. There were no complaints from the use of other batches of the same preparation.

The family history of the infants was negative for allergy except

that the father had infrequent attacks of angioedema. The past history of the infants was essentially negative from every standpoint. The authors answered the question which must be uppermost in the mind of every physician who has read their report, as follows: "In view of the high mortality which accompanies both diphtheria and pertussis during infancy, it is hoped that the publication of these two fatalities will not deter the profession from continuing to practice immunization."

A fatal allergic reaction to influenza vaccine has been reported by Curphey (2). This occurred in a three and a half-year-old girl. There was no family history of allergy. The child had had hives for one day during her first year of life thought to be due to aspirin. There was no history of sensitivity to egg or chicken. Four hours after the subcutaneous injection of 0.5 cc. of stock influenza type A and B vaccine, the child developed fever, chills, vomiting and convulsions. She was hospitalized within two hours after the onset of symptoms but died five hours later, despite all efforts at therapy. At necropsy the whole picture was suggestive of reaction to a foreign protein rather than an allergic reaction in the ordinary sense, since such manifestations as asthma and urticaria were lacking. The author recommended that in the administration of such vaccine an intradermal test should be done with small doses of the antigen, and if local reactions occur, the immunization should be done by the successive injections of small doses at short intervals. This would doubtless protect satisfactorily against the action of the vaccine *per se* as an allergen in the case of children with whom greater precautions must be taken because they react more frequently to egg protein than do adults.

Salk (5), in commenting upon this report, has made some remarks which appear equally applicable to the cases reported by Werne and Garrow (6) and described above. Salk stated that toxic reactions to vaccine are proportional in frequency and severity to the concentration of the virus injected. In Curphey's case the findings appeared to Salk to be more in accord with a toxic reaction to the virus than to an asymptomatic allergy to some egg constituent in the vaccine. Since the frequency and severity of reactions are related to virus concentration, it would seem reasonable to consider a reduction in the concentration of virus in vaccine for use in children. The dose of virus can be varied over a rather wide range with little influence on mean antibody response in groups given different doses. It might

be suggested that caution be exercised in the use of influenza vaccine not only with respect to sensitivity to egg constituents but with respect to the dose of virus given to young children.

Ratner and associates (3, 4) have made extensive studies with regard to the relationship between allergic reactions and the egg protein content of viral and rickettsial vaccine. They stated that because of the avidity that rickettsiae and viruses have for embryonal tissue, the chick embryo was found to be a desirable culture medium for the preparation of immunizing vaccines. The vaccines which are presently considered of value as immunizing agents are yellow fever, typhus, Rocky Mountain spotted fever, or tick typhus, equine encephalomyelitis, influenza A and B strains of virus, and mumps. However, allergic reactions have resulted from the use of vaccines in sensitive persons. These authors found that 20 per cent of 500 allergic children demonstrated hypersensitivity to egg protein on skin testing. In only 5 per cent was this sensitivity of clinical significance. They concluded as a result of their studies that because egg proteins are found in viral and rickettsial vaccines, the use of such vaccines in egg sensitive persons may result in allergic episodes, encompassing the entire gamut of allergic reactivity. A direct relation was found between allergenicity and the chick-embryo-protein content of the vaccines. Thus red-blood-cell-eluate vaccines containing the greatest amount of egg protein elicited greater reactions than centrifuged or alcohol-precipitated vaccines, the latter perhaps being the least allergenic.

Ratner and associates evaluated the criteria for determining the allergic hazard prior to therapeutic use of vaccine as follows:

1. An intradermal injection of 0.02 cc. of the vaccine is of prime value in determining the degree of sensitivity.
2. If a systemic reaction follows it is evidence of a high degree of sensitivity. The vaccine should then be withheld or given in small diluted or fractionated doses, preferably intradermally in conjunction with several minims of epinephrine.
3. If only a large local reaction ensues with a test dose, the vaccine can be diluted and administered with 2 minims of epinephrine.
4. A history of sensitivity to egg, while valuable, is not as reliable a criterion as the intradermal test with the vaccine itself.

No reactions were noted in several hundred non-egg sensitive allergic children repeatedly given injections of influenza and mumps vaccine. Reactions in certain non-egg sensitive children were shown to be due to the formalin incorporated in the vaccine. They believe that the allergic hazards and unnecessary deaths which have resulted from the use of virus and rickettsial vaccines can be eliminated (1) by the reduction of egg-protein content in such vaccines, (2) if due regard is given to the criteria discussed above for determining sensitivity prior to the administration of such vaccines, and (3) if due caution is exercised in the use of these vaccines in egg-sensitive subjects.

REACTIONS FOLLOWING ANTIRABIES PROPHYLAXIS

The neurological complications of antirabies prophylaxis have been discussed in Chapter 50. The study of Blatt and Lepper (1) indicated that of 2,193 persons treated with antirabies vaccine over a two-year period, sixteen (an incidence of 1:131) developed complications. Seven of these reactions involved the nervous system and will not be further considered here (see Chapter 50). Of the other eight, the most constant symptom was fever which was present in all patients. Other initial symptoms were radicular pain, local erythema and induration, malaise, headache, and generalized weakness.

Blatt and Lepper stated that the signs and symptoms of antirabies vaccine reaction which indicate that therapy should be discontinued are: Occurrence of an otherwise unexplained fever, paresis, and radicular pain or headache. However, any complaint obviously not due to another disease must be considered potentially dangerous. An intradermal skin test, using antirabies vaccine diluted 1:10, was found to be positive in all patients in whom a clinical reaction to rabies vaccine developed, but was positive in 60 per cent of all patients being vaccinated. Persons not vaccinated with rabies vaccine gave negative skin tests.

Blatt and Lepper suggested that ACTH may be of value in treating patients who develop reactions to antirabies vaccine. It would seem to me that, if the reaction rate is as high as they reported, the prophylactic use of cortisone or hydrocortisone or ACTH at the time the vaccine is being given might be a highly useful procedure.

While the physician should be aware that untoward and serious

reactions may occur following prophylactic injections, in comparison with the millions of injections given the reactions are exceedingly infrequent except in the case of antirabies vaccination. Very rarely a patient who has heard of such an incident will inquire of the physician as to the danger to his particular child of the usual prophylactic injections. My reply commonly is: "You drove to the office with the child in an automobile, didn't you? The chances of injury to your child from taking such a risk are infinitely greater than the chances of harm from the injection I am about to give him." The good to be done in the prevention of disease so far outweighs the possibility of harm from a practical standpoint that the risk need not even be considered. However, the proof of any pudding lies in the eating thereof. In over twenty years of practicing pediatric allergy as a specialty, giving the routine injections to the new babies as they came along and insisting on adequate prophylaxis for the older children, I have never had a reaction which I felt in any way seriously endangered a child or was followed by any persistent disability (see also Chap. 66).

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THE ANTIHISTAMINES

THE PLACE of the antihistamines in allergic practice is now well established and it is the purpose of this chapter to point out only a few features of these drugs of particular importance to allergy in pediatrics. For a complete and concise discussion of the antihistaminics as a whole, reference is made to the book by Feinberg and associates (3).

Early in the use of these drugs it was believed that the antihistaminics of different chemical groups might prove more valuable in some forms of allergic disease than in others. However, as time went on it became obvious that these drugs are highly selective in their action in individual cases and that while one drug might give great relief from the symptoms of pollinosis, for example, in one patient, in another with the same condition the same drug would be useless or even deleterious. Therefore, each trial of an antihistaminic drug in an allergic patient is always an experiment. If it does not help the patient, it is justifiable to try successive preparations until an antihistaminic is found which will accomplish its purpose if the patient can be relieved by any antihistaminic whatsoever. The question that is so frequently asked, "Doctor, what is the very best antihistaminic?" may be answered: "The best antihistaminic in your case is the one that works best for you." There is no other accurate answer.

DOSAGE OF THE ANTIHISTAMINIC DRUGS

One of the first reports on the treatment of allergic diseases in children was that of Logan (7) who employed Benadryl and suggested a 4 mg. per kg. (2 mg. per lb.) of body weight as a single dose. It soon became recognized, however, that the dose of an antihistaminic drug necessary for an adequate therapeutic effect depended to a great degree on the severity of the allergic reaction. Such a quantitative reaction might reasonably be expected since in

the more severe reactions more histamine is liberated. For example, in the treatment of serum sickness in children varying in age from two months to eight years Peterson and Bishop (8) administered single doses as high as 8 mg. per lb. to small infants and these authors felt that it might take two or three times as much per unit weight to control symptoms in infants as in adults. However, there is an upper limit to a dose which will produce a therapeutic effect and in no case was it necessary to give more than 100 mg. a day for the relief of serum sickness in these children.

TOXIC REACTIONS TO THE ANTIHISTAMINES

This subject has been thoroughly reviewed by Wyngaarden and Seevers (10) and more recently by Judge and Dumars, Jr. (5). The former report that different agents may possess side effects of varying degrees, the incidence of such reactions ranging from 10 to 63 per cent. In general, antihistamine intoxication resembles that of atropine. Usually the more severe reactions occur with higher doses but even a small dose may produce a reaction in a susceptible individual. Wyngaarden and Seevers also pointed out that the usual side reaction of these drugs in children is stimulation though depression may occur and that the susceptibility of children to the convulsant action of these drugs is striking and impressive. The ability to withstand overdoses appears to increase with age, and the older the patient the more does the toxic manifestation change from that of central nervous system stimulation to that of depression. Convulsions can, however, occur in the adult.

Wyngaarden and Seevers (10) tabulated eight fatal cases in infants two years of age or less. Included in their series is the case of Davis and Hunt (2) who reported death in a two-year-old child following the accidental ingestion of 474 mg. of Benadryl. The principal symptoms were cyanosis, convulsions, cardiorespiratory depression and hypothermia. Necropsy showed findings similar to those of heat stroke, with thymic and epicardial petechial hemorrhages and cerebral edema, pulmonary congestion and edema, and passive congestion of the liver and kidneys.

An important untoward reaction to the antihistaminic drugs in childhood which cannot be classified as particularly toxic or dangerous occurs much more frequently than is generally suspected and

often remains undiagnosed. This is a change in the personality of the child which has been briefly discussed by Schaffer (9). This change may also occur in adults but with not nearly the frequency that it does in children. Schaffer tabulated the cases of twenty-three children who were being treated by the antihistaminic drugs for various manifestations of allergy. The children varied in age from two to ten years and at least three different kinds of antihistaminic drugs were employed, four if Benadryl plus aminophyllin (Hydryllin) is considered as a different drug than Benadryl alone. The most common symptom was irritability; crying or weepiness, perverseness or disobedience, loss of appetite and indifference also occurred. With cessation of the offending antihistaminic there was a complete reversal to the normal state in two or three days.

Another interesting and less frequently observed unusual reaction to the antihistaminics is the quieting of fetal movements in utero which has been noted both by Davison (1) and Glaser (4). The subsequent newborn infants in my experience have, however, not been harmed because of this.

TREATMENT OF ANTIHISTAMINE INTOXICATION IN CHILDHOOD

Unfortunately there is no known specific antidote at the present time for antihistamine intoxication. The best treatment is prophylaxis and, as Lecks (6) pointed out, these preparations, many of them attractively colored, should be kept out of the reach of children. While it is possible that antidotal therapy with ACTH and/or cortisone may be very useful in antihistamine intoxication, as in other forms of poisoning, the use of these drugs for this purpose has not yet been reported.

Lecks has recommended the following procedures:

1. Evacuation of the stomach contents. If the child is unconscious particular care must be exercised to avoid aspiration pneumonia. If the child is not too somnolent an emetic could be tried.

2. If the child is convulsing, ether anesthesia may be used. This may either be given by mask or by rectum with equal parts of olive oil ($\frac{1}{2}$ to 1 cc. per kg.) Paraldehyde rectally with an equal amount of olive oil (4 to 5 cc. as an initial dose) may be used instead. If these measures fail, short acting barbiturates in repeated small doses

may be helpful. Long acting barbiturates and particularly narcotics should be avoided because of possible late respiratory depressant effects.

3. For a coma or stupor, amphetamine sulphate, 5 to 10 mg., should be given intravenously or intramuscularly and repeated at intervals depending upon the response and the age of the patient. Caution should be used since convulsions may be precipitated by overdosage. Other stimulants such as ephedrine sulphate (5 to 10 mg. per kg.) and caffeine (10 mg. per kg.) may be used if amphetamine is not available for parenteral use.

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PREVENTION OF ALLERGIC REACTIONS TO DRUGS

ONE OF THE more common questions put to the allergist is the possibility of preventing allergic reactions to drugs in the various procedures where iodine compounds are used for diagnostic purposes. This includes intravenous and subcutaneous urography, the intravenous dyes for visualizing circulation, bronchography and the intraspinal injection of contrast media. If it is not an emergency procedure, I commonly advocate a trial of a saturated solution of potassium iodide orally for a few days. The adult dose is 10 drops of a saturated solution well diluted in water or milk three times a day after meals, and children in proportion. While a negative reaction to this test would not rule out the possibility of an untoward reaction to parenteral iodine, it appears to be satisfactory as far as bronchography is concerned. A positive reaction such as a rash, rhinorrhea, swelling of the salivary glands, a gastrointestinal or other disturbance, would certainly contraindicate the use of iodine compounds for contrast purposes in any case.

Simon, Berman, and Barald (5), following the work of Getzoff (3), have reported very favorably on the use of chlortrimeton malleate, an antihistaminic, in the prevention of reactions to intravenously injected iodine contrast media. They used 2.5 cc. of a solution equal to 5 mg. of chlortrimeton malleate mixed with the contrast media. One cc. was injected intravenously as a test dose, and with the needle in the vein a pause of approximately one minute was made. If no adverse reactions occurred the injection was given quite rapidly.

The successful use of ACTH and cortisone in the treatment of drug reactions was reported early by Carey and associates (2), and this naturally suggests its use in the prophylaxis of drug reactions including iodism following bronchography. Such cases have been reported by Theddos (6) and by Park and associates (4). It would

seem reasonable that the steroids should be given prior to the administration of any drug where the consequences of a severe allergic reaction might be serious. I have often recommended giving 50 to 75 mg. of cortisone orally or by injection or 20 units of ACTH gel eight hours before operation and repeating the dose an hour before the operation, planning to continue with this medication should a drug reaction ensue. Despite this regime some immediate mild drug reactions have occurred. However, further studies in this field are highly necessary before a final decision can be made.

LOCAL ANESTHETICS

The problem not infrequently arises, especially in dental practice, as to whether or not it is safe to give an allergic child a local anesthetic. Fortunately reactions to these preparations are very infrequent in pediatric practice and unfortunately there is no satisfactory skin test for such anesthetics. My procedure, which has not been used in enough cases as yet to determine its definitive value, does not depend upon skin tests but upon a modified clinical test with the drugs.

The dentist is requested to forward to the office with the patient a vial of the drug which he would like to use in that particular case. Serial dilutions are then made in normal saline. If there is no reason for the testing other than the presence of a known allergic disorder three dilutions of the drug are commonly made, viz.: $1/10$, $1/100$, and $1/1000$. If the patient has experienced disagreeable reactions to local anesthetics in the past, still further dilutions may be made, up to $1/1,000,000$ or even greater.

The patient is then allowed to rest comfortably in a chair and his pulse and blood pressure are recorded. He is given a subcutaneous injection of 0.10 cc. of the local anesthetic in the solution of maximum dilution into one arm. An equal amount of normal saline is injected into the other arm. The patient's clinical reactions are carefully observed and at the end of ten minutes his pulse and blood pressure are again noted. If he appears to have experienced no disagreeable effects he is then given an injection of 0.25 cc. of the same dilution into the opposite arm from the first injection of the anesthetic and an equal volume of normal saline into the other arm. The patient is again carefully observed for ten minutes and his blood

pressure and pulse again taken. If there has been no disagreeable reaction, 0.75 cc. of the anesthetic is injected into the alternate arm with the usual saline control in the other arm. If no untoward reactions ensue, the same procedure is repeated with the 1/100 dilution and then the 1/10 dilution and finally the undiluted anesthetic just as the dentist wishes to use it. In event no immediate disagreeable effects are noted one should wait twenty-four hours for the appearance of delayed reactions before pronouncing the anesthetic safe for use.

It is important to remember that the local anesthetics often contain epinephrine which may not infrequently cause disagreeable reactions (palpitation, nervousness, pallor, tremor, etc.) which may be mistaken for reactions to the anesthetic. If this is suspected then the patient must be tested with the epinephrine alone.

If it can be shown that the particular anesthetic which the dentist had planned to use is not suitable for the patient, then he can often choose one of another chemical group to which the patient may not be sensitive. There may be, in some instances, an overlapping allergy in the different groups, but very often this is not sufficient to prevent the use of one or the other of these drugs. According to Adler *et al.* (1), the local anesthetics, other than procaine, are chiefly derived from these chemical groups: (1) benzoic and oxybenzoic acid as Metacaine (piperocaine); (2) phenol, as phenocaine hydrochloride (Holocaine); (3) cinnaminic acid, as apothesine hydrochloride; (4) isoquinoline, as Nupercaine hydrochloride (Dibucaine), and (5) derivatives of xyloidine, as xylocaine (Lidocaine).

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CHAPTER 49

ANAPHYLACTOID PURPURA

(The Schönlein-Henoch Syndrome)

FROM a practical standpoint, according to Clement and Diamond (9) the symptom complex of purpura may be divided into three major groups as follows: (1) symptomatic or definitely secondary purpuras associated with a variety of recognizable disease entities; (2) nonthrombopenic or vascular purpura having as a probable basis a disturbance involving the capillaries alone, possibly a sensitization phenomenon, and usually called the anaphylactoid, allergic, or Schönlein-Henoch type, and (3) the thrombopenic form of purpura hemorrhagica, not associated with a recognized primary cause and therefore usually labeled idiopathic.

Clement and Diamond (9) further stated that purpura with and without thrombopenia has long been regarded by some observers as a hypersensitivity phenomenon and has been found in association with classical manifestations of allergy in a significantly high number of patients. Positive family histories for allergic manifestations were found in eleven of forty-four nonthrombocytopenic patients (25 per cent). Personal manifestations of frank allergy in this group of patients were found in thirteen (30 per cent). In the thrombopenic cases the family history was positive for allergy in twenty-nine patients (30 per cent). Personal manifestations of frank allergy in the low platelet group of patients were noted in fourteen (15.5 per cent). If both groups are combined, positive family histories are found in 35 per cent, and personal manifestations of allergy in 20 per cent. These figures are well above the expected incidence of allergy in families encountered in the clinic of Clement and Diamond.

This chapter will be concerned only with anaphylactoid purpura, which is also termed the Schönlein-Henoch syndrome, as this is the form of purpura of most interest to the allergist. Gairdner (11), who reviewed this subject exhaustively and reported a series of cases of his own, prefers to use the eponym "Schönlein-Henoch syndrome"

(hereinafter designated as SH) rather than the term "anaphylactoid purpura." This is due to the fact that we are not yet completely clear on the relationship of this disease to allergy and anaphylaxis and because purpura is neither uniformly present nor is it the essential histological feature of the exanthem as will be presently discussed.

Gairdner (11) stated that the SH syndrome is composed of three main groups of symptoms: (1) a specific exanthem; (2) gastrointestinal symptoms, as colic, vomiting and hemorrhage, and (3) arthritis. Recurrences of one or more of this triad are characteristic and hematuria is common. The disease was recognized as an entity in 1837 when Schönlein named the combination of joint symptoms with a rash "peliosis rheumatica," the word peliosis meaning livid. Henoch (1874) reported a series of four cases in children with a rash, colic, bloody diarrhea, and painful joints. Later he emphasized the frequent association of nephritis. Krauss (1883) showed that this condition differed from purpura hemorrhagica (Werlhof's disease—1775) in that the platelets are not reduced in the SH syndrome. Osler (1914) called attention to the analogies between the SH syndrome and serum disease. He stated that some forms of purpura are anaphylactic phenomena. Frank (1915) first used the term "anaphylactoid." Glansmann (1920) recognized that both infection and sensitization were involved. Alexander and Eyermann (2, 3) drew attention to the possible etiologic factor of food sensitization.

The disease is most common in males and chiefly occurs between the ages of three and fourteen years. The first lesions, as far as the rash is concerned, are typically small hives occurring discretely upon the extensor surfaces of the upper and lower limbs. At this stage they are somewhat itchy. Within a few hours they begin to change to pink maculo-papules becoming less raised and darker in color. By the following day they have become dusky red macules which do not fade on pressure. Their size is from 0.5 to 2 cm. in diameter, but some may coalesce to form larger patches. There is a slow regression from this stage, the red color becoming more purple before fading to brown and finally disappearing altogether by the end of two weeks. Three sites are most commonly effected: (1) buttocks and lower back; (2) backs of elbows and extensor surfaces of arms and legs, and (3) extensor surfaces of the lower legs, ankles and feet. Small, isolated red spots are occasionally seen in

the buccal mucosa but bleeding from the mouth and nose does not occur. The lesions are roughly symmetrical but are usually more marked on the arm which is most used.

The word "purpura" means "purple" and has come to be used for any red or purple lesions which do not fade on pressure and which are assumed to be due to hemorrhage. The red macules of the SH syndrome derive their color and its persistence on pressure from hemorrhage. Histologically an acute aseptic inflammatory reaction around the vessels of the corium with frequently a tissue eosinophilia, forms the basis of the exanthem of the SH syndrome. Necrotizing arteritis, which has been found on occasion in the skin, gut and brain, presumably represents a severe degree of the same process. The skin histology is unlike that of similar appearing lesions in other diseases except for erythema annulare. This is significant because that is a rheumatic exanthem.

Gastro-intestinal symptoms are commonly present and may mimic appendicitis and intussusception and may occasionally initiate the latter. Melena is often present. If gastro-intestinal symptoms occur before the rash, laparotomy is often performed and the principle finding is local edema and often hemorrhage into the wall of the gut. The terminal ileum is the segment most commonly effected. The alimentary lesions of the SH syndrome have been particularly studied by Balf (6), who reported on a series of twenty cases seen over a period of two years at the Royal Hospital for Sick Children in Edinburgh. He stated that the bowel lesions are transient and have never progressed to chronic bowel disease. In three cases which came to operation the intestinal lesions were essentially similar. Each segment of the bowel affected was sharply separated from the normal tissue. The mesentary and bowel were edematous and of an intense scarlet color. There was no suggestion of such discoloration of the bowel as might have been expected had there been interstitial bleeding. Despite the acute inflammatory erythema, the process did not extend to adjacent coils of gut. On each occasion a descriptive diagnosis of acute regional enteritis was made at operation and later developments raised doubt as to the true diagnosis. In the fourth, a similar, though not as severe, clinical course was accompanied by evidence of disordered peristalsis. In the fifth case this peristaltic disturbance appeared to have induced a true

intussusception. None of these five cases appeared explicable in terms of mucosal purpura. The intestinal lesions could best be explained by a sub-mucosal shunt with intense local spasm diverting the greater part of the blood flow to the outer layers of the bowel.

One of the above cases may be regarded as rather typical. A boy, ten years old, was admitted as an abdominal emergency with severe, colicky, abdominal pain and vomiting. He had had a transient rash on his chest eight days previously and two days later slight diarrhea for three days. At the time of admission there was diffuse tenderness of the left hypochondrium and the bowel sounds were absent. On exploratory laparotomy there was free fluid in the abdominal cavity. The jejunum was acutely inflamed, bright red and edematous. The segment involved was sharply separated from the normal bowel. There was complete obstruction and it was necessary to do a posterior gastrojejunostomy. The boy was readmitted about two and a half months later with typical SH purpura and later developed melena and severe abdominal pain.

Pratt (23) stated that, "no one should operate on a child with abdominal colic until the diagnosis of Schönlein-Henoch's disease has been excluded." Intussusception is apparently more frequently simulated than any other abdominal surgical condition. Althausen, Deamer, and Kerr (4) stated that the following points may be helpful in the differential diagnosis: Four out of five patients with intussusception are under two years of age, whereas the SH syndrome may occur at any age; abdominal tenderness and spasm, which are often found from the time of onset of pain in the SH syndrome, rarely occur between attacks of colic until twenty-four hours or more after onset of intussusception; hemoptysis is practically never seen in intussusception but may occur in the SH syndrome, and severe and persistent tenesmus is a very important symptom of intussusception and is usually absent in the abdominal SH syndrome. Bailey (5) pointed out that where there is a possibility that one is dealing with an abdominal emergency of this character one should look for the purpuric spots which always maximally aggregate on the extensor surfaces. When the trunk alone is involved the differential diagnosis is more complex. In doubtful cases the tourniquet test should be applied. It is, however, unfortunately true that intussusception *may* result from involvement of the bowel in the SH

syndrome. This subject was reviewed by Brust (8) who reported a case of gangrenous intussusception in a two-year-old girl who had most of the extra-abdominal evidence of the SH syndrome. Survival followed operation.

Nephritis is common and is often the most serious aspect of this condition. Hematuria, gross or microscopic, is commonly present. This may go on to recovery or to chronic nephritis or to rapidly developing renal failure and death. Of Gairdner's twelve cases of the SH syndrome with nephritis, only seven recovered fully so that the outlook for this may possibly be serious. Microscopically glomerulonephritis is present but tubular degeneration may occur. There is a special tendency for hematuria to continue over a long period of time without the development of hypertension or other signs of nephritis.

Philpott (20), in 1952, reported a series of forty cases of the SH syndrome in children. Males predominated in the ratio of five to three and throat infections preceded the disease in 55 per cent of cases. Two cases occurred in children under one year of age. Nineteen, or 47 per cent, developed nephritis. Of these Philpott was able to follow eleven and the nephritis was still active in four after one year.

The incidence of allergy in Gairdner's series, unlike that of Clement and Diamond (9) was insignificant. However, the fact that nephritis may occur as part of the picture of the SH syndrome due to allergy to food is very well documented.

Brown (7) noted a boy nine years of age who suddenly developed hematuria as a result of the SH syndrome. By means of elimination diets, tomato was incriminated and positive skin tests to tomato were obtained on two occasions. No further attacks occurred after the elimination of tomato from the diet but three months after the last attack red blood cells and casts were still present in the urine.

Kittredge (15) described a boy eight years of age who had hematuria of four years duration. There was no history of any preceding illness. He drank milk freely with nearly every meal and consumed as much as a gallon a day. An elimination diet consisting only of milk increased the hematuria. Skin tests were negative. Later it was shown that he could tolerate boiled but not raw milk. The boy had a history of urticaria, epistaxis, headache, and one attack of poly-

arthritis but no purpura. This case suggests that any patient with idiopathic hematuria should be studied from the standpoint of the SH syndrome. This is also indicated by the report of Levitt and Burbank (18). Elimination diets rather than skin tests are the most effective diagnostic measures.

Lazarus (17) reported an eighteen-year-old boy who since the age of fourteen had had four episodes of hematuria associated with pain in the lower back, groin and thigh. Subconjunctival hemorrhages and arthralgia effecting several joints accompanied the above symptoms. Other conditions having been ruled out he was studied from the standpoint of allergy and found sensitive to rice, wheat, chocolate, nuts, and some vegetables and fruits. Elimination of these foods resulted in prompt and complete disappearance of all symptoms.

It is also possible that a combination of allergens of different types may cause the SH syndrome whether accompanied by nephritis or not. Piraino (22) described a three-year-old girl whose chief symptoms were abdominal pain, melena and a purpuric rash. Penicillin was suspected as the chief causative factor with sensitivity to egg probably playing a secondary role.

A great variety of other allergens may also be responsible for allergic purpura as has been so splendidly documented by Ackroyd (1). Purpura following vaccine injection is rare. Such a case was described by Freud and Greenberg (10) in a year-old infant following an injection of pertussis vaccine. Jelke (14) described a case following the injection of diphtheria antitoxin in a three-year-old girl. Siegel and associates (26) reported a three-year-old girl with purpura following mosquito bites successfully treated with cortisone.

Despite all the above evidence in favor of various etiological agents as causes of this disease, I believe it is a fair statement to say that in most instances the causes remain unknown.

The joint symptoms of the SH syndrome are frequent and, according to Gairdner (11) vary from transient puffiness of a single joint to recurrent painful swellings of many joints. Pain is rarely as severe as in rheumatic fever nor is the joint so tender to touch or movement. Pains do not appear to be well relieved by salicylates and fever is low grade, rarely above 37.7 C. (100 F.). The blood picture shows no characteristic features. Capillary resistance is commonly normal. In two of Gairdner's cases, the SH syndrome

was closely associated with rheumatic arthritis. However, involvement of the heart does not appear to be frequent in the SH syndrome.

TREATMENT OF THE SCHÖNLEIN-HENOCH SYNDROME

Until the advent of cortisone and corticotropin (ACTH) there was no satisfactory treatment for this disease. Philpott and Briggs (21) used these drugs in nine cases with no dramatic results. They did not prevent relapses in the condition nor onset of nephritis in three of seven cases; neither did they have any effect upon the course of the nephritis. They were not convinced that the drugs are of value in this disease. Stefanini and associates (27) were perhaps the first to use ACTH successfully in the SH syndrome. Their patient was a three-year-old boy with severe purpuric manifestations. However, ACTH did not prevent the development of a mild glomerulonephritis. Kugelmass (16) noted good results in four children, two of whom had hematuria. Hork (12) found cortisone satisfactory in a twenty-one-month-old boy with the skin and oral mucous membrane manifestations of the disease. My own personal experience with three older children, two of whom had abdominal manifestations besides those involving the skin and none of whom had nephritis were highly satisfactory. Further study, however, is indicated with special reference to the prevention and treatment of the nephritis occurring with the SH syndrome.

ACTH and cortisone also appear to be helpful in the treatment of idiopathic thrombocytopenic purpura (13, 24), but this does not indicate an allergic origin for this disease.

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NEUROALLERGY IN CHILDHOOD

WHILE the role of allergy in the production of neurological symptoms is still somewhat controversial, if one considers the fundamental pathological physiology of allergic disease, edema or spasm of smooth muscle, or both occurring together, it would be strange indeed if allergic reactions did not occur in the nervous system. These tissues do have a blood vessel supply and wherever blood vessels are found, even though the smooth muscle may be scanty in some areas, edema may occur. Since this is true, Karnosh's (5) remark in discussing the psychosomatic aspects of allergy, appears very reasonable: "It becomes more and more apparent that the reaction (allergic) involves every level of the nervous system from the highest and most elaborate centers of the cortex to the humblest sympathetic terminal and capillary loop of the skin." Evidence since accumulated, particularly in the reports of Davison (2) and Dees (3, 4) have amply justified this statement.

Dees (4) stated that the majority of central nervous system reactions due to allergy have been reported in adults not because children have less vulnerable nervous systems than adults but because children are less articulate in describing sensations and situations which vary from their usual state. Furthermore, neurologic examination is more difficult and often more cursory in children than in older people. Dees further noted that in allergy involving the central nervous system as with allergy elsewhere, the allergic stimulus may require reinforcement by nonspecific factors such as fatigue, chilling, infection, psychogenic stimuli, trauma and others. The nervous system has certain fixed reaction patterns to various stimuli and the same response may be elicited both by allergenic and non-allergenic causes in the same person. For these reasons, it may at times be difficult to prove the allergic nature of the symptoms and signs involving the central nervous system.

Cranial and peripheral nerve palsies, convulsive disorders, meningitis and headache and behavior disturbances are the diseases which

are best authenticated as having, in some instances, an allergic etiology. Less well documented are certain of the encephalitic syndromes such as follow small pox vaccination, measles, other infectious diseases and certain degenerative diseases of which multiple sclerosis is the best example.

Serious neurological sequelae occasionally occur as a result of prophylactic inoculations. Miller and Stanton (6), who reviewed the literature of this subject, classified the resulting clinical syndromes into four main overlapping groups: (1) radiculitis including radiculoneuritis, mononeuritis, plexitis, and shoulder girdle neuritis; (2) polyneuritis and polyradiculoneuritis (Guillain-Barré syndrome); (3) myelitis and Landry's ascending paralysis, and (4) meningeal and cerebral forms. The majority of the neuritic and radicular conditions recover in from a few months to two years. About 20 per cent of the patients are left with some residual weakness and wasting. The cerebral and myelitic forms carry a graver prognosis.

Miller and Stanton stated that the complications of pertussis vaccination are different from those encountered after other prophylactic inoculations in that they are always cerebral. In one case reviewed by them, hemiplegia on the right side followed an apparently acute cerebral illness seven days after a third injection of diphtheria-pertussis vaccine, leaving moderate residual disability two years later. In another case convulsions and stupor followed twenty-four hours after a second injection of diphtheria-pertussis vaccine, but recovery was complete and rapid. Transverse myelitis occurred in one instance following inoculation against diphtheria, with appreciable disability persisting nine years later. Probably the most interesting case reviewed was that of a ten-year-old boy who, after a Schick test, developed an acute bulbar encephalopathy. He recovered but on examination seven months later showed wasting and weakness of the temporal and masseter muscles. Miller and Stanton suggested that the common factor in the pathogenesis of these cases is anaphylactic hypersensitivity and that a similar mechanism may be involved in many of the identical neurological illnesses that occur independently of preceding inoculation. They also made the interesting observation that the distribution of lesions varies with each inoculum, and shows some correspondence with that seen in the relevant infection.

NEUROLOGICAL COMPLICATIONS OF ANTIRABIES PROPHYLAXIS

The neurological complications of vaccination against rabies are also believed to result from hypersensitivity reactions. Their incidence has been reviewed by Turnauer (8) who reported a variation between an upper limit of 1:2200 and a lower limit of 1:7000. The incidence of complications appeared to depend to a large degree on the method of preparation of the vaccine, most complications occurring with the fresh virus and least with the heat treated virus. Her review also indicated that although 50 per cent of all treatments are given to children, they show neurological complications relatively infrequently.

A much more pessimistic report was made by Blatt and Lepper (1) who studied the findings among 2,193 persons in Chicago who received antirabies prophylaxis with a rabies vaccine prepared by ultraviolet irradiation of rabbit brain containing rabies virus during the years 1950-1952. Seven of the patients developed evidence of involvement of the nervous system as a complication, a ratio of 1:313 or 0.3 per cent. It is significant that of eight such patients, four were children between the ages of six and twelve.

Turnauer quoted Remlinger, who appears to have studied the largest number of patients with neurological complications, a series of 243, to the effect that the most common was severe paraplegia with bladder and rectal involvement which occurred in about 28 per cent of cases; the next most common was Landry's ascending paralysis which constituted about 16 per cent of the complications. Others included various forms of paralysis of the lower extremities and cranial nerves, bladder involvement and miscellaneous neuritis.

Other types of complications to rabies vaccination have been discussed elsewhere (see Chapt. 46).

MENINGITIC SERUM REACTIONS

Ratner (7) has differentiated three types of meningitis following serum injections: (1) serum sickness meningitis; (2) aseptic or serum meningitis, and (3) allergic meningitis.

Aseptic or serum meningitis results from the primary contact of the meninges with the serum after intrathecal injection. It is non-

allergic and polymorphonuclear cells are predominant in the spinal field.

Allergic meningitis may be a sequel to intrathecal injection of serum in a person who has been sensitized by previous injection of the serum. It also is characterized by the presence of predominantly polymorphonuclear cells in the spinal fluid but coupled with this sign are profound allergic reactions of the nervous system.

Serum sickness meningitis resembles clinically serous meningitis which occurs in infancy and childhood commonly as a result of infection. It follows the injection of serum, usually by the extrathecal route and manifests itself during the course of ordinary generalized serum sickness. The spinal fluid shows a predominance of lymphocytes.

According to Ratner, the cerebral symptoms of serum allergy may be characterized by choked discs, meningeal irritation, the Kernig and Babinski signs and by such additional manifestations as aphasia, alexia, hemianopsia and hemiplegia, and various disorders of the cranial nerves. Such reactions may not only occur from serum but also from various drugs, vaccines, foods and other allergens. Antibiotics have now largely replaced serum in the treatment of meningitis and Dees (4) has noted similar reactions complicating their use in combined intrathecal and intramuscular therapy.

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ELECTROENCEPHALOGRAPHY IN ALLERGIC CHILDREN

Dees and Lowenbach (2) were stimulated to study the electroencephalograms of allergic children because of their observation of the high incidence of symptoms referable to the central nervous system in these children. An allergic group of eighty-five children ranging in age from two to fourteen years was compared with a large control group. All major forms of allergy, except physical allergy, were represented. Twenty-two patients had a convulsive disorder (petit or grand mal) for which no immediate cause could be demonstrated. These authors made a practice of performing tests for allergy on all patients with cryptogenic convulsions whose personal or family history suggested the possibility of an allergic disorder.

Occipital dysrhythmia was present in forty-two of the eighty-five children, or about 50 per cent of the group. In the sixty-three children without convulsive disorders, occipital dysrhythmia was present in twenty-nine (45 per cent). The overall percentage of predominantly occipital dysrhythmia was 59 per cent in the convulsive group. A positive family history for allergy was associated with occipital dysrhythmia twice as frequently as was a negative family history. No similar preponderance of occipital dysrhythmia occurs in normal children in their experience. The type of EEG change is unrelated to the kind of allergy, the duration of the disease, or positive or negative family history. The occipital dysrhythmia was not confined to any one allergic condition and there seemed to be no difference between patients with single or multiple allergic disorders.

In thirty-six patients, repeated EEGs were made at various intervals, usually three months to four years. The records were unchanged in twenty-five and showed improvement in eleven. All patients whose EEGs had improved showed improvement in their allergic condition but clinical improvement was found in some without significant change in the EEG.

Chobot and associates (1) studied eighty children from an allergy clinic (aged two to fourteen years) which was heterogenous as regards to sex, diagnosis and severity of the illness. Of eighty encephalograms, fifty-four were completely normal (67 per cent) and twenty-six (32.5 per cent) abnormal. Of these abnormal children,

twenty-one were given a course of an antihistaminic (Trimeton) and the EEG repeated. Only one returned to normal.

Chobot and associates concluded that there is a high incidence of abnormal EEG patterns in allergic children (about 33 per cent of their series as compared with 50 per cent in the Dees and Lowenbach (2) series). Similarly a high incidence of abnormal patterns was found in the families of allergic children. There was a definite preponderance in the girls over the boys. An apparently increasing incidence of abnormal patterns with increasing duration of allergic symptoms appeared to be present. Chobot and associates, in agreement with others, found no relation between the clinical types of allergy and the EEG pattern. They were not impressed with the significance of occipital dysrhythmia alone since they state it is observed very commonly in clinically normal children when the remainder of the EEG pattern over the frontal and parietal areas is well within normal limits.

Holmgren and Kraepelien (4) studied 100 asthmatic children and unlike Dees and Lowenbach excluded all with a known hereditary predisposition for convulsive disease, or who showed signs of a convulsive disease, or who had a history of birth injury or known cerebral injury later. It is quite significant that in this series they found an incidence of about 33 per cent of abnormal EEGs, just as did Chobot and associates. Their work suggested that pathological EEG occurs with greater frequency in more severe asthma than in mild cases. They were unable to establish a correlation between the duration of disease and the occurrence of EEG changes as did Dees and Lowenbach and Chobot and coworkers. However, like Dees and Lowenbach and also DeToni (3) an occipital dysrhythmia was found to occur in the great majority of the pathological cases. In this connection it is interesting that Dees and Lowenbach (2) also found as previously mentioned, a high incidence of occipital dysrhythmia in children with convulsive disorders and some of these patients suffered from epilepsy of allergic origin.

In a control series of 150 normal children of about the same age group as the asthmatic children Holmgren and Kraepelien (4) found only about 5 per cent of dysrhythmic EEGs, a figure largely in agreement with others studying normal children. It thus appears that asthmatic children show a much greater frequency of EEG

changes than normal children but there is no satisfactory explanation as to why.

Sternbergh and Baldrige (6), in a very limited series of twelve patients, presumably adults, with generalized neurodermatitis (chronic atopic dermatitis) of four to fifty years duration who were chosen to exclude patients who had other conditions which might influence the EEG, found only three who showed normal EEGs.

Dees and Lowenbach state that the occurrence of abnormal cerebral potential may offer an explanation for the clinical observation that allergic children so frequently present personality problems. It is possible that a great deal of such behavior might be explained by a central nervous system that does not function smoothly and efficiently. It is highly probable that their somewhat higher incidence of EEG changes was due to the fact that there were so many children with convulsive disorders in their series.

It is possible that as knowledge of encephalography progresses the EEG may eventually be of assistance in differentiating allergic epilepsy from idiopathic epilepsy. Jasper (5) showed one tracing of allergic encephalopathy with epilepsy showing diffuse slow and sharp waves with some bilaterally synchronous sharp-slow sequences at about 2 to 2.5 sec. which he stated are common in diffuse encephalopathies of various etiology and should be clearly distinguished from the EEG of idiopathic epilepsy.

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EPILEPSY

Credit for the suggestion that allergy might be a cause of epilepsy is generally given to Spratling (16) who in 1904 suggested that

sensitivity to food might be an important factor in some cases. However, as to whether or not this actually occurs has been looked upon with skepticism by such prominent allergists as Vaughn (17), who felt that the evidence precluded any great degree of enthusiasm for allergy as a cause of epilepsy, and by Feinberg (9), who stated his belief that epilepsy occurring along with atopic manifestations is probably pure coincidence. Bridge (2), in his book on convulsive disorders in children, stated that in 742 cases of epilepsy seen by him he had encountered no incidence of food as a cause of convulsions, although he noted that this had been reported, giving only two references. Cooke (5) wrote that, although a certain number of cases with convulsive seizures undoubtedly represent an allergic cerebral reaction, this does not mean that idiopathic epilepsy in general is to be regarded as one of the diseases of allergy.

However, in 1952, Davison (6) published the first really complete review of the literature of this subject. He collected the reports of 110 patients with allergic epilepsy and in addition noted sixty-seven personal cases. There can be no doubt whatsoever from Davison's impressive documentation that epilepsy of allergic origin (including petit mal) does occur more frequently than is generally appreciated. Some of the more interesting of the many references from the standpoint of pediatric allergy are as follows:

Kennedy (11) reported one case of epilepsy in a child with urticaria which was relieved by omitting milk from the diet. Spangler (15) mentioned a fifteen-year-old boy who had convulsions after eating veal and a nine-year-old girl who had gastrointestinal symptoms and epilepsy after eating eggs; Bowen (1), a boy thirteen years of age with attacks of epilepsy due to milk and wheat; Clarke (4), three patients whose epileptic attacks were caused respectively by wheat in the first patient, by milk in the second, and by wheat and milk in the third; and Pleasants (13), an epileptic child whose attacks were caused by milk.

Dees (7) has found helpful the following modification of Forman's (10) criteria for suspecting allergic epilepsy:

1. Family or personal history of allergy.
2. Eosinophilia preceding and during attacks.
3. Positive skin tests.
4. Absence of demonstrable organic brain disease.
5. Characteristic EEG pattern of occipital dysrhythmia.

In a group of thirty-seven allergic children with convulsive disorders of the grand or petit mal type Dees and Lowenbach (8) found that occipital dysrhythmia was a predominant abnormality in 73 per cent of the cases. In a control series of twenty-three non-allergic children with convulsions only two, or less than 10 per cent had occipital dysrhythmia. In the allergic group of thirty-seven, anti-allergic measures were followed with such good control of convulsions in twenty-four patients that complete withdrawal of sedatives was possible in twelve patients.

Dees (7) has not found antihistaminics effective in controlling seizures in allergic children, even though they may completely relieve other allergic symptoms. Dees and Lowenbach (8) occasionally showed transient improvement in the EEG in children with convulsive disorders of allergic origin, treated with antihistamines. Churchill and Gammon (3) (age of patients not stated but presumably adults) found that the two antihistaminic drugs studied, diphenhydramine (benadryl) and tripelenamine (pyribenzamine), were both capable of inducing seizures in epileptic patients with focal lesions of the cerebral cortex. However, tripelenamine increased petit mal seizures while diphenhydramine had the opposite effect. Their studies indicate that these drugs should be given with care to adult allergic patients with convulsive disorders. Fortunately this does not appear to be the case with children.

Inhalant allergens also apparently may cause epileptic convulsions. Rowe (14) reported one child, four years of age, with asthma, headache, mental and emotional symptoms, and convulsive attacks, all relieved by injections of extracts of pollens to which the child was sensitive. Levin (12) described a three-year-old girl who was proven to be sensitive to cat hair and had no epileptic attacks unless contact with cat hair occurred.

The impression gained from Davison's review is to the effect that when epilepsy is caused by foods, milk, egg and wheat are most common allergens, just as might be expected from general experience with allergy due to foods. Unfortunately, skin tests for foods, as in most instances of food allergy, are not particularly helpful so that one must resort to elimination diets.

It is not the intent of this discussion to imply that epilepsy (includ-

ing petit mal) is commonly an allergic disease. It doubtless is not. However, allergy should be considered as a possible cause of this condition, especially when Forman's (10) criteria are present.

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MIGRAINE*

BY THE TERM "migraine" is meant the periodic occurrence of headache, commonly unilateral, which may be associated with visual disturbances and/or a variety of other symptoms and is usually accompanied or followed by nausea and vomiting. The mechanism of migraine is doubtless vascular in origin, as indicated by the original observations of Goltman (8) and Wolff (31).

The incidence of migraine in allergic children now appears to be reasonably well documented. In a series of 516 successive allergic children seen in my practice at the age of ten years or less, migraine occurred in 1.16 per cent of cases, which was, curiously, exactly the same percentage of children who had severe reactions to insect bites. Stoesser and Nelson (25) in 750 allergic children up to the age of eighteen years, found migraine in 1.7 per cent of cases. London (16) in a study of the composition of the first 1500 cases seen in an average pediatric practice, reported headache in eleven patients, (migraine was not specified) an incidence of this symptom of about 1.4 per cent. From these and other sources (6), it is concluded that the incidence of migraine in the general pediatric population is probably somewhat less than 1 per cent and in allergic children not over 2 per cent. As age advances migraine occurs more frequently, menstrual migraine probably adding significantly to this figure, so that the incidence of migraine in the adult population is probably close to 7 per cent (1, 28). Studies as to the incidence of migraine in allergic adults have not as yet been published.

A review of the evidence indicates that there is a strong hereditary factor in migraine (6). Balyeat and Brittain (1) in a study of fifty-five patients with migraine reported that a hereditary factor was present in 85 per cent. Vahlquist and Hackzell (29) also found hered-

* Most of the material for this chapter has been taken from another publication by the author (6) and is in part reproduced here by permission of the copyright owners.

ity an important factor but noted that in twenty-six families with severe migraine in one or another of the parents, only three out of forty-three children (7 per cent) of an average age of seven years manifested signs of this disease. They therefore stated that it would seem that migraine in one of the parents does not necessarily bring about early onset of the disease in the offspring. About the only conclusions one can draw from the study of heredity is that migraine may occur whether or not there is a past personal or family history of allergy. About the only importance one can attach to a family history of allergy is that when present it suggests that allergy is more likely to be a factor in the disease than when not present, but a negative history by no means rules out an allergic etiology. There appears to be no significant difference in the sex incidence in children (6).

The age of onset of migraine in infancy and childhood is of considerable interest. The question, therefore, naturally arises as to how one can diagnose headache in infancy and early childhood. According to Plant (20) in young infants, headache may be suggested by wrinkling of the forehead, rubbing of the head, restlessness, and crying. The diagnosis appears to be established by observing the pattern of behavior which the infant or very young child exhibits during the attack. If, when the child grows older and can describe his symptoms, he complains of headache when exhibiting this same behavior pattern, it seems quite reasonable to suppose that headache was also present before he became old enough to complain about it.

Russell (23) reported a boy, first studied at the age of thirteen years, who suffered from migraine and ophthalmoplegia where the evidence indicated that the attacks had started when the patient was only two weeks of age, probably the earliest onset on record.

Vahlquist and Hackzell (29) noted the case of a boy whose mother had menstrual migraine. This child's first attack occurred at the age of one year when he suddenly turned pale and had an attack of vomiting. During the next two years he had several attacks a week, always of the same type. When he was about three years of age he began to complain of pain in his head during the attacks. Another was a boy whose first attack started at the age of two and one-half years. This consisted of a left-sided hemicrania usually associated

with nausea and sometimes vomiting, and, on one occasion, vertigo. The attacks generally occurred when he was tired or cold.

Balyeat and Rinkel (2) gave the protocols of three cases of patients where migraine started in one instance at the age of one and one-half years and in two others at the age of two years. In the majority of Hecker's (13) cases the illness began between the ages of six and ten years. In one instance, however, the first attack occurred when the child was one and one-half years of age and in five between the ages of two and three years.

The youngest child I have ever seen with typical migraine was a girl three years of age. She would act as though in pain, would pat one side of her head and constantly repeat the single word "hurt." These attacks were followed by abdominal pain, nausea and vomiting. However, the complaint for which the child came to the office was bronchial asthma and migraine was elicited only in taking a detailed history. The few cases of migraine which I have seen in children five years of age or less have all been diagnosed by careful history taking, as the child came to the office for some other condition. That this state of affairs is not unusual is borne out by the findings of Balyeat and Rinkel (2) to the effect that at the time their article was written, they had under their care a number of migrainous children under five years of age, all of whom came, not on account of headaches, but for relief of allergic syndromes.

The psychogenic element appeared to Vahlquist and Hackzell (29) to be of major importance. The majority of the children were said by their parents to be sensitive, nervous, and of uneven disposition with various behavior disturbances such as nail biting. Attacks were precipitated by such factors as nervous tension, insufficient sleep, irregular meals, fatigue, exposure to bright sunlight, and moving pictures. In view of the latter, it will be interesting to note the effect of television on these patients. Krupp and Friedman (15), in 1953, reported a series of fifty children between the ages of three and fifteen years and stated that practically all gave some evidence of psychogenic disturbance and recommended psychotherapeutic and symptomatic treatment. Allergy was not mentioned as a possible etiologic factor. Unger and Unger (26) have concluded that although in their opinion migraine is basically an allergic disease, psychic stimuli may produce attacks in allergic individuals.

The major symptoms of migraine in children and adults are very similar but there are certain differences, both as regards the prodromal symptoms and the attack (6). One of the principal differences is that in young children abdominal pain may accompany migraine and the younger the child the more likely it is that the abdominal component will overshadow the cephalic component. The headache in young children may be a minor symptom but increases in severity as the child grows older, the adult type being fully developed at about the age of twelve years. In my experience, also, the headache is less likely to be unilateral than is the case with adults.

Another principal difference from adults is that migraine in children may be accompanied by fever, although this has not been a significant finding in my own experience. However, according to Riley (22), temperatures as high as 39.4 C. to 40 C. (103 F. to 104 F.) may be encountered. Since abdominal pain and fever do not occur in migraine in adults, these symptoms in children may draw attention away from the diagnosis of migraine to an explanation of the subsequent abdominal pain, nausea and vomiting as heralding the onset of an acute infection, and acute abdominal surgical conditions such as appendicitis have been suspected (14). One should always rule out migraine in a child who has abdominal pain, whether or not accompanied by fever, if headache, however mild, is also present. The diagnosis of an acute abdomen requiring surgical intervention under such circumstances should always be confirmed by the customary ancillary measures.

While visual disturbances may occur in young children, they are not as common as in adults. Dees (4) states that such symptoms rarely occur under eight or nine years of age. She believes that this absence is probably due to the child's inability to describe these strange sensations and because of our tendency to get the history from the parents and not directly questioning the child, rather than to the fact that they do not occur in children. If we listen to the child, he may state that he sees "bees" or "flies" or "lights," or indicates that he has diplopia, and these symptoms should alert the physician to the possibility of migraine.

The physical examination, except for evidence of pain or malaise and the laboratory tests are completely negative. Dees (4) reported that children have been observed to gain weight rapidly just prior to

headache and to lose it just as rapidly as the headache wanes. Diuresis or enuresis may be present at this time. Moench (19) stated that rapid weight gain followed later by polyuria also occurs in adults and is particularly striking in those cases associated with premenstrual tension. Dees has also noted that the EEG with spiky wave changes which has been observed in adults has not been reported in children, probably because records have not been obtained during or in the prodromata of a headache.

The prognosis for migraine of early onset, according to Vahlquist and Hackzell (29), does not appear to be especially unfavorable. The frequency of attacks was said to be diminishing in twenty out of twenty-two patients who had passed the age of seven years. One of the patients who was over fifteen years had been completely free from symptoms for seven years and four of the others had had at the most three or four attacks a year.

In the differential diagnosis of the symptom complex of headache, abdominal pain and or nausea and vomiting, one must consider the numerous possible causes of these symptoms (21). Riley (22) has stated that in any child presenting symptoms of an obscure character located in the abdomen, careful investigation should be made into the past and family history in order to determine the presence of any tendency toward the development of migrainous episodes. In this connection, because of the well-known occasional relationship between migraine and epilepsy, the so-called "abdominal epilepsy" must be considered. This condition has been reviewed by Blumberg (3) who stated that the criteria for diagnosis are the ruling out of organic pathology as the cause of the abdominal pain, a positive electroencephalogram and the therapeutic response to anticonvulsive drugs.

One of the most common causes of recurrent headache in children in my experience has been errors of refraction, and this can produce the symptom complex of migraine. Grunert (12) stated that in 129 patients with migraine under the age of fifteen years, he was able to relieve the symptoms by proper ophthalmological supervision. In my opinion, no child with headache should be given up as hopeless from the standpoint of relief other than by symptomatic remedies, until he has been completely refracted by a truly competent oculist. I have studied two children diagnosed as migraine

who obtained apparent cures by this procedure only following the prolonged occlusion test of Marlow (18) which is very time-consuming but in selected cases may reveal the cause of otherwise intractable cephalgia. In this connection cyclic vomiting should be mentioned. This symptom complex, which has been noted by practically all students of the subject, notably Smith (24) and Vahlquist (27), as an occasional precursor of migraine, is, in some instances, unquestionably due to food allergy (5). However, the few cases of cyclic vomiting referred to me for study from the standpoint of allergy did not, in the instances where relief was obtained, receive this as a result of such studies but through the correction of errors of refraction (7).

Another important cause of headache simulating migraine, and particularly in children with allergy involving the nasal mucous membranes, may be obstruction of the sinus ostia by allergic edema of these membranes producing, because of the absorption of the air within the sinus, the so-called "vacuum headache." Occasionally headaches of this type may be easily diagnosed by relief following the use of vasoconstrictive nose drops, or occasionally the oral administration of an antihistamine preparation. There are also other types of headaches due to allergy which do not fulfill the criteria for the diagnosis of migraine.

It should be clearly understood that the thesis of this chapter is not to the effect that all migraine in children is due to allergy and particularly food allergy. There are doubtless a number of other causes but the allergist, because of the nature of his practice, is more likely to encounter a preponderance of patients who have migraine of allergic origin. From the standpoint of the allergist there is little doubt but that migraine may be produced by foods. While the knowledge that certain individuals may suffer severe headaches following the ingestion of certain foods is probably as old as recorded history, it was not until 1927 that Vaughn (30) reported on a series of controlled studies in adults which proved this point, and Balyeat and Rinkel (2), in 1931, drew attention to foods as a cause of migraine in childhood. Goltman (8) has stated that inhalants are the main factors in allergic migraine in adults. I have seen no reports of, nor had any personal experience with inhalant allergens as the cause of migraine in children, but that might be because inhalant factors have

not been given sufficient consideration in this age group. In my experience with children the most common foods producing migraine have been chocolate, egg, wheat, and milk. Although my own series is too small to be definitive, Unger and Unger (26) working mostly with adults reported somewhat similar findings, with chocolate as the most common offender, followed by milk, wheat, and pork. Skin tests have been of no value in my experience, the offending foods, when not already known by experience, have been commonly found by means of elimination diets. It seems reasonable to suppose, therefore, that the allergens causing the attacks are intermediate metabolic products of these foods, the nature of which is unknown and for which, therefore, no skin testing materials are available.

SYMPTOMATIC TREATMENT OF MIGRAINE

The medications employed for the symptomatic relief of migraine are the same as those used in adults with modification of the dosage according to the age and weight of the child. Also, as in the case of adults, the sooner the medication is given after the onset of the attack the more satisfactory it commonly is. The most effective drug for the relief of migraine is ergotamine tartrate and a child about six years of age, who commonly has severe attacks, should be given a 1 mg. tablet with half a glass of water immediately at the onset of an attack and this dose repeated in another half-hour if not relieved. For the mechanism of action of ergotamine tartrate, reference is made to the report of Graham and Wolff (11). Occasionally Caffergot, a combination of 1 mg. of ergotamine tartrate with 100 mg. of caffeine, administered in the same manner, may be more effective. In the adolescent group, if the smaller doses do not help, two tablets may be taken at the onset and one at half-hour intervals until relief, or until a total of six tablets has been taken for each attack. Caffergot suppositories, which contain 2 mg. of ergotamine tartrate and 200 mg. caffeine have proven of significant help in adults and would probably be of help in children. Graham (10) has pointed out that if for any reason the rectal preparations are not available, the tablets may be used effectively rectally. Parenteral preparations of the same medications are also available.

Aspirin occasionally gives good relief but it is sometimes necessary to use codeine or demerol. Phenobarbital, epinephrine, ephed-

drine, the antihistaminics and dilantin sodium have been of no help in my experience. A sedative mixture* has been very effective in some cases. It would seem that ACTH or cortisone, if given at the very first aura of an attack, might be helpful in migraine of allergic origin, but acceptable studies concerning this have not yet been published.

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Sedative Elixir (Fellows)—each 5 cc. (teaspoon) contains 0.5 gm. (7½ grains) each of chloral hydrate and calcium bromide and 0.125 mg. (1/480 grain) of atropin. The adult dose is 1 to 2 teaspoons with milk, fruit juice or water repeated every three or four hours as necessary. Children according to age and weight.

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ALLERGY TO INSECT BITES AND STINGS

ALLERGY to insects may occur in one of three ways: (1) by the inhalation of emanations of insects, as the scales, scent, etc.; (2) by contact with insects, and (3) by insect bites and stings. This chapter will be concerned only with the last group since this appears to be by far the most important in children. The literature of the entire subject of allergy to insects has been reviewed by E. A. Brown (5) up to the year 1944. Since then progress has been made chiefly in the direction of more adequate treatment as will be discussed below.

The incidence of allergic reactions to insect bites and stings was 1.6 per cent in 516 allergic children ten years of age or less when first seen in my practice; curiously, this is exactly the same as the incidence of migraine. The insects most commonly involved are bees, wasps and mosquitoes although others may, at times, cause similar difficulty. Bowen (3) has tabulated twenty-five different kinds of insects to which allergy has been reported. Probably the most common form of allergy to insect bites is papular urticaria, most commonly due to fleas, which has been discussed previously. Urticaria from bed bug bites is also well known.

The first sting of an insect may act as a sensitizing dose so that subsequent stings may produce allergic reactions, as has been described by Jex-Blake (12) in the case of bee stings. It is, however, also true that subsequent stings at times appear to possess the property of hyposensitizing the individual. This has been documented by Kemper (13), and the phenomenon of the child, who early in the season reacts violently to mosquito bites and later is not particularly troubled, is well known. Baker (1) has contributed the interesting suggestion that possibly in some parts of the world where insects and insect eggs are considered a delicacy in the diet, such foods may be responsible for the acquisition of sensitivity to insects.

The symptomatology of allergy to insect bites and stings, which is complicated by the normal physiological reaction of the individual

to the toxin of the insect venom, may vary considerably in degree. The milder symptoms are localized pain, pruritis and edema, followed by urticaria or angioedema which may be local or general. The more severe symptoms are dyspnea, which may be asthmatic or due to edema of the larynx; cyanosis; allergic rhinitis; gastrointestinal symptoms such as nausea, vomiting and cramps and involuntary defecation; involuntary urination; and frothy or bloody sputum or both, followed by gradual recovery or death, usually within a period of minutes rather than hours.

Death from insect bites and stings has not been reported in children with nearly the frequency that it has in adults but does occur. Hobson (10) described a seven-year-old boy who died twenty minutes after receiving thirty to fifty wasp stings. There was no history of the child's having been stung before. Bowen (3) reported a death from ant stings after a period of about twenty-nine hours. Brown and associates (4) discussed in considerable detail a non-fatal Arthus phenomenon of long standing due to mosquito bites in a fifteen-year-old girl.

The autopsy findings of death from bee stings have been described by Schenken and associates (18) who reported a case of their own and reviewed nine others found in the literature. One of these was a girl six years of age, the only case of death from bee sting with an autopsy reported in a child. The most frequent findings were laryngeal edema with obstruction, acute pulmonary emphysema and edema, cerebral edema and visceral congestion. Jex-Blake (12) also noted dilatation of the right side of the heart.

The prophylaxis of insect bites includes the use of protective netting, smudges of various types and local applications to the skin such as oil of citronella, for example. This subject has been discussed by Goldman (8). These are, however, very often not satisfactory, particularly in the case of an active child. Shannon (19) recommended the administration of thiamin chloride by mouth as a prophylactic measure against mosquito bites, and reported in detail a number of interesting cases in which this remedy was highly efficacious. The mechanism of action of the thiamin has not been satisfactorily explained. Thiamin is excreted onto the skin, probably by the sweat glands, imparting to the skin its characteristic odor, and it has been thought that this is perhaps what keeps away the mos-

quitos. However, in one case where Shannon employed a 3 per cent thiamin chloride ointment no protection was obtained.

Eder (7), following the lead of Shannon, successfully used thiamin chloride for flea bites and recommended the following dosage schedule: Small infants, 10 mg. three times a day for three days; then 10 mg. or as much more as may be found necessary, daily for several weeks. A runabout child is given twice as much, and an adult three times the infant dose. I have used this schedule for mosquito bites in my practice for a number of years with reasonably satisfactory results in about half the cases though dramatic successes have occasionally occurred.

The symptomatic treatment of insect bites and stings has been completely revolutionized in recent years, first in the case of the less severe reactions by the advent of antihistaminics and more recently in the case of the more severe reactions by ACTH and cortisone.

If the sting is of any significance it is my practice to apply a tourniquet, if the sting is on an extremity, above the injury and, in any event, to inject into the site from 0.5 to 1.0 cc. of 1 per cent procaine (which has an antihistaminic as well as an anesthetic action). If the reaction to the sting is severe an injection of epinephrine 1/1000 is also made into the site of the sting. If a tourniquet has been used, another injection should be made into one of the other extremities. The patient is then given an antihistaminic orally in full doses every four hours until the effect of the injury has worn off. Meantime the tourniquet is released periodically.

If the patient is known to have suffered severe allergic reactions to insects in the past, or if such a reaction appears to be developing, the same procedure is used but, in addition, a large dose of cortisone, not less than 100 mg., is given orally and repeated in doses of 50 mg. every six hours for twenty-four hours; then every eight hours for twenty-four hours, and then gradually reduced as the allergic reaction subsides or comes under control. If the patient is vomiting the cortisone may be given by intramuscular injection. ACTH may be used instead of cortisone, with an initial dose of 60 units of the aqueous preparation and half that given in six hours, and the same dose repeated every eight hours thereafter, gradually tapering off in the same manner as described for cortisone. It is unlikely that steroid treatment will have to be continued long enough so that disturb-

ances of electrolyte metabolism and other adverse reactions to these drugs will have to be considered.

James and Walker (11) reported the case of an eighteen-month-old boy who received 477 wasp stings and was treated with ACTH and other agents. However, because such a multiplicity of therapy was used it could not be concluded that the ACTH was responsible for the boy's recovery. Siegel and associates (20) noted a three-year-old girl who developed anaphylactoid purpura as a result of mosquito bites. She responded nicely to cortisone.

Cluxten (6) recorded the successful use of ACTH in the treatment of a black widow spider bite in an adult by a single intramuscular injection of 40 units of ACTH, and another successful result in the case of a woman bitten by a copperhead snake who required several injections. Maretić (14) also described the bite of a spider (*Latrodectus tridecimguttatus*) successfully treated by the injection of a single dose of 80 mg. of cortisone.

It is well for individuals who suffer reactions to carry with them an antihistaminic drug and cortisone at all times. I also teach the parents how to inject adrenalin in order to save time awaiting the arrival of a physician.

The pioneer work in the field of hyposensitization against insect bites and stings was initiated by Benson and Semenov (2) in 1930. The stings of bees and wasps are by far the most important from the standpoint of the physician. This subject has been thoroughly studied and brought up to date by Mueller and Hill (17). The bees belong to the aphid family and the wasps to the vespid family of the order hymenoptera. The social species of both are the most important since members of the solitary species are not ordinarily stingers. Mueller and Hill state that, although the fact is not entirely clear, the sensitizing antigen seems to be contained in the entire body of the insect. It is likely that there are multiple antigens and that some are species specific and some are generic specific. Although cross reactions probably occur, there has been no completely convincing study of cross-sensitivity.

The degree of sensitivity may be fantastically great. McLane (16) noted the case of a woman who was so sensitive to whole bee extract that the injection of 0.065 cc. (one minum) of a 1:1,000,000 dilution caused urticaria and wheezing. She was, however, eventu-

ally successfully hyposensitized. With respect to sensitivity of this character, Swinney (21) made the practical observation that if a person is found dead during the summer months, and the cause of death cannot be readily determined, the possibility of death from an insect sting must be considered, especially if there is a history of previous stings with severe reactions.

The protection conferred by hypimmunization may not be permanent. Wolf (22) reported a man who had been successfully hypimmunized against wasp stings to the extent that for a year after treatments were stopped he was stung several times with only negligible reactions. However, eventually these reactions gradually became worse and the patient planned to resume treatments. This was not done and he eventually died as the result of a sting.

Following the recommendations of Mueller and Hill (17) for treatment by hyposensitization, I use a mixture of equal parts of the extract of bee, yellow jacket, and wasp. Hornet extract will be added when this becomes available. The treatment materials may be obtained from allergy supply houses and the appropriate dilutions prepared, or the supply houses will prepare treatment sets as requested. The dosage schedule of Mueller and Hill (slightly modified), which I now follow, is recorded in Table XX.

TABLE XX
SUGGESTED DOSAGE SCHEDULE (CC.)

<i>1/1,000,000</i>	<i>1/100,000</i>	<i>1/10,000</i>	<i>1/1000</i>	<i>1/100</i>	<i>1/10</i>
0.05	0.05	0.05	0.05	0.05	0.05
0.10	0.10	0.10	0.10	0.10	0.10
0.20	0.20	0.20	0.20	0.15	0.15
0.40	0.40	0.40	0.30	0.20	0.20
			0.40	0.30	0.30
				0.40	0.50

Slightly modified from Mueller and Hill (17).

Mueller and Hill suggest doing an intracutaneous test with a 1:1,000,000 dilution of the antigen and if the test is negative to begin treatments with 0.10 cc. of this dilution. However, if the test is completely and unequivocally negative, I commonly test with the next dilution, 1:100,000 and if that is negative to the 1:10,000 and if this is negative start with that dilution, following the schedule in Table XX.

Injections are given once or twice a week until a dose of 0.30 cc. or 0.40 cc. of the 1:10 dilution is reached. This is then given once a month for three years. My experience with this procedure, and a similar procedure which was employed prior to the publication of Mueller and Hill, has been highly satisfactory.

Hypimmunization has also been used successfully against other insects. McIvor and Cherney (15) used flea antigen for a three-year-old girl who suffered from asthmatic attacks accompanied by urticaria, believed to be due to flea bites. During the clinical trial of the flea antigen the child received a series of injections, each resulting in an asthmatic episode. She is said to have been greatly benefited by the treatments.

Hatoff (9) reported immunizing 129 susceptible infants and children at an average age of four years against flea bites by the injection of extract of the whole fleas of cat, dog, and human being. Of these 78 per cent were benefited; 5 per cent received equivocal benefit, and 17 per cent failed to respond. Each of these children had had unabated symptoms for a period of one week to one year.

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OCULAR ALLERGY

ALLERGY of the eye, except for conditions involving the skin and subcutaneous tissues of the lids, such as atopic dermatitis, contact dermatitis, urticaria, and angioedema, does not play a very important part in the allergic diseases of childhood. The only exception to this is conjunctivitis, due in most instances to pollen, which may on rare occasions be the sole presenting symptom of pollinosis. It is also possible that conjunctivitis may occur as the sole manifestation of allergy to other inhalants besides pollen or to food, drugs, and bacteria but such cases are certainly very uncommon. This subject has been discussed particularly by Bowen (1). Occasionally non-allergic factors, such as irritation from chlorine in swimming pools or epidemic conjunctivitis ("pink eye") must be ruled out, but this problem presents no special difficulties. In the series of 516 children reported by McKinney and Glaser (7), allergic conjunctivitis occurred in not quite one per cent of the series as a problem worthy of being recorded in the diagnostic file, and other possible allergic conditions occurred even less frequently. Ocular allergy will, therefore, be only briefly reviewed in this discussion. For a very comprehensive consideration of allergy of the eye reference is made to the splendid chapter on this subject by Urbach and Gottlieb (11). Only a limited number of the conditions dealt with by them will be mentioned here.

VERNAL CONJUNCTIVITIS

Vernal Catarrh

On rare occasions the pediatric allergist may have the opportunity of studying this condition, commonly with unsatisfactory results. Duke-Elder (4) has given the following comprehensive definition of this disease: "Vernal conjunctivitis is a recurrent bilateral, interstitial inflammation of the conjunctiva, of seasonal incidence and (as yet) unknown etiology, characterized by flat-topped papules

usually on the tarsal conjunctiva resembling cobblestones in appearance, a gelatinous type extrophy of the limbal conjunctiva, either discrete or confluent, accompanied by corneal involvement, and associated with itching and redness of the eyes, lacrimation, and a mucinous or lardaceous discharge usually containing eosinophils." It is more common in children than in adults. There are two types of this disease, namely, the limbic and the lid form. The former is usually localized on the bulbar conjunctiva near the limbus, appearing as vesicles which may coalesce to form gray crescentic or annular lesions. The palpebral type is divided into simple follicular, the pavement epithelium (cobblestone), and the granuloma or giant cobblestone forms.

Urbach and Gottlieb (11) have reviewed the various theories which are strongly suggestive that this is an allergic condition. However, while the disease does appear to be of allergic origin, there is no convincing evidence concerning the nature of the responsible allergens. A review of the literature since their publication did not contribute any particularly new information. The confused state of affairs with regard to this disease is indicated by the implication of many factors, such as endocrinological, even incriminating the thymus gland.

The only really worthwhile recent contribution to therapy in this disease was the introduction of cortisone and hydrocortisone eye drops and ointments which appear to be the most beneficial form of therapy as yet employed.

Taub and associates (10) reported nineteen patients with superficial punctate keratitis of allergic etiology. One of these was a three-year-old girl in whom orange, kapok, and tomato were incriminated. She had complete relief of symptoms and no recurrence when these allergens were eliminated. I have had a similar problem in a seven-year-old girl successfully managed by treatment with pollen and house dust extract.

Hogan (5) has reviewed the evidence that kerato-conjunctivitis may at times be an allergic disease and reported a case in a boy six-and-one-half-years of age who had suffered from intractable eczema since infancy; his eyes had always been slightly watery, hyperemic and itchy, and he had been troubled with rhinitis and asthma since five-and-one-half-years of age. He was relieved by

topical cortisone acetate suspension. There was, however, no report of a detailed study of this boy from the standpoint of allergy, and the relief by cortisone does not prove an allergic etiology. However, Hogan believes that atopic kerato-conjunctivitis is a specific entity because of its occurrence in patients with associated allergic diseases and variation in intensity with the allergic eczema.

Iritis and uveitis, which occasionally occur in children, may on very rare occasions in adults be due to food allergy as indicated by the reports of Parry (8) and Roch (9). Bothman (3) had presented evidence to the effect that dust and molds may sometimes play a part. Most commonly the disease is probably due to focal infection or bacterial allergy. The methods for diagnosing the etiological organisms and the treatment have been described by Woods (12).

Kimura and associates (6) reported on eighteen cases of anterior uveitis in children. In twelve of these the etiology could not be determined. The only frequent findings were an allergic diathesis in seven cases and a constant eosinophilia in two others, suggesting that allergy may be an important factor. Skin tests and serologic tests were consistently negative except in two cases, one with a positive Brucella skin test but a negative serologic test; the other with a positive tuberculin test. The allergic method of approach was not further discussed.

It is now well known that cataract may occur on rare occasions in young adults who have suffered for a long time with chronic atopic dermatitis. It appears not earlier than the second decade of life although it may make its appearance much later, and is unilateral in about a third of the cases. This disease has been briefly reviewed by Bentolila and associates (2) who noted such a cataract in a woman twenty-one years old who had suffered from chronic atopic dermatitis since four months of age.

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CHAPTER 54

PHYSICAL ALLERGY

WHEN PHYSICAL agents are spoken of as producing allergic reactions, the following are usually meant: (1) mechanical stimuli, such as pressure and friction; (2) cold; (3) heat, and (4) light (8). The first group has been discussed previously under the term, *dermographia*. A variety of skin disturbances due to light sensitization may occur in children, as *hydroa estivale*, *solar eczema*, *summer prurigo*, *solar urticaria*, and *xeroderma pigmentosum* (1). These diseases are, however, more the province of the dermatologist than the allergist. So far as I am aware, allergic reactions to heat have not been described in children. Physical allergy in children, as far as the allergist is concerned, is therefore chiefly a problem of urticarial reactions to cold.

Salter, according to Harkavy (9), first reported physical allergy in 1860 when he noted a case of asthma induced by the application of cold to the instep. Bourdon and Bahier, independently in 1866, according to the review of Kelly and Wise (11) also reported on this condition. It was, however, not until Duke (6), in 1923, described a case of urticaria due to light that studies were initiated, chiefly by Duke, which have done so much to increase our knowledge of these conditions. It should also be mentioned in passing that many reactions other than urticaria or angioedema of the skin and subcutaneous tissues have been ascribed to cold. These are edema of the glottis, diarrhea, visual disturbances, purpura, non-infectious disease of the paranasal sinuses, which may be attributed to localized urticaria in the nasal membranes, myalgia involving the muscles of the head, nausea, vomiting, irritable bladder, arthralgia, vertigo, and hemoglobimuria, as indicated in the review of Kierland (12). Cryoglobulinemia has also been associated with allergy to cold as noted by Steinhardt and Fisher (17) who reviewed the literature and reported a case in a woman. Whether or not physical allergy represents true allergy in the sense that it is medi-

ated by an antigen-antibody reaction is a disputed question concerning which reference is made to the work of Kierland (12).

There are but few specific case reports of physical allergy in children and all of these were due to cold.

Bray (2), in 1932 and again in 1935 (3), reported an eight and one-half-year-old boy whose hands would become pink, swollen to twice their size, and pruritic following immersion in cold water. Some hours later he would develop a cough and coryza. This subsequent reaction could be prevented by a tourniquet around the cold hand. It is interesting that the mucous membranes were unresponsive since the sucking of ice did not cause swelling or irritation. The boy was treated by injections of histamine, a total of 16.2 mg. having been given in a series of twenty-five injections over a period of twenty-seven days. An older and a younger brother suffered from asthma.

Watrin (18) mentioned a girl eleven years of age who, following an attack of urticaria from eating strawberries at the age of ten years, thereafter reacted with papular urticaria on areas of the skin exposed to cold.

Covisa and Prieto (5) described a boy seen at the age of two and one-half years because of scabies complicated by pyoderma who starting two months previously would erupt with hives when his skin was exposed to cold. The authors reported that this reaction was successfully passively transferred.

Another interesting case, not documented in any detail, was that of a boy eleven years of age who, when exposed to the slightest chill, as from an electric fan, would react with nasal obstruction followed by cough (14).

Kobacker and Parkhurst (13) reported urticaria due to cold following measles in three sisters, eight, eleven, and thirteen years of age respectively. Physical examination and laboratory findings were negative except for eosinophilia of 7, 10, and 13 per cent respectively.

Rodin and Bluefarb (16) described a four and one-half-year-old girl suffering from cold urticaria. The disorder appeared soon after birth. The family history demonstrated that this condition had been present in twenty-one members and spread over four generations, suggesting that the disorder is a dominant non-sex linked Mendelian

trait. In this particular patient all the laboratory tests including passive transfer and cold agglutinations were negative.

Of particular interest with respect to these problems are the observations of Kelly and Wise (11) who reviewed the several instances in the literature of inherited allergy due to cold and made the interesting discovery that these patients differ from the majority of instances of urticaria due to cold as follows: Symptoms begin in infancy; cold air results in generalized urticaria, joint pain, and fever; pruritis is not associated with the wheals, and local application of ice water does not result in a reaction.

Zum Busch (4) has described his own case. He stated that he had been sensitive to cold since childhood; that his nose ran when exposed to a draft; on putting his foot out of the warm bed he would suffer nasal discharge and sneezing; immersion of the hands in cold water would cause redness, swelling and itching. Several times while swimming he experienced sudden weakness so that he could reach the shore only by a supreme effort, and this was followed by collapse and an eruption of giant urticaria about the joints. A similar reaction developed once in a cold air bath. He made the interesting remark that this hypersensitiveness might be present only at times.

Kaufman (10) studied the problem of a boy first seen at the age of twelve years because of various allergic symptoms, among others the appearance of urticaria where his skin was exposed to cold. Sucking on a piece of ice would cause enormous swellings of his tongue and lips. All the allergic symptoms, including those due to cold, disappeared when egg was omitted from his diet.

Aside from allergies to cold such as asthmatic attacks as well as various nasal manifestations, I have seen but one child with severe cold allergy. This was a boy who at the age of two years suffered from recurrent attacks of fever, nasal discharge and behavior disorders. These attacks occurred intermittently in the cold weather and the mother, a very keen and intelligent observer, began to realize that they were associated with exposure to cold. Removal of the tonsils and adenoids at the age of three years did nothing to relieve his difficulties. I saw him at the age of seven and one-half years in consultation with Dr. Donald D. Posson at the Strong Memorial Hospital where allergy to cold was diagnosed. An attempt

was made to hyposensitize him by means of cold hand baths (see Table XXI). This appeared to give some relief but had to be done very carefully.

An attempt was made to hyposensitize him by injections of histamine with an initial dose of 0.10 cc. of a 1:50,000 dilution

TABLE XXI
COLD HYPOSENSITIZATION

Use ice water at 10° C. (50° F.) and immerse both hands well over the wrists. Use a thermometer to determine temperature of the water.

- 1st week—twice daily for 1 minute
- 2nd week—twice daily for 2 minutes
- 3rd week—twice daily for 3 minutes
- 4th week—twice daily for 4 minutes
- 5th week—twice daily for 5 minutes

If improvement is then satisfactory, you may try taking the baths once a day; if you continue satisfactorily, try taking the baths every other day; if this is satisfactory, try by experimentation to find out how often you must take the baths to remain well.

If by the fifth week you feel you are improving but have not improved sufficiently, increase by one minute a day until the baths are taken ten minutes twice a day. If then relieved, proceed as in paragraph immediately above; if not relieved, discontinue treatments and consult Dr. Glaser.

(histamine base) following the schedule indicated in Table XXII. Immediately following the injection he developed fever, stupor and collapse, but revived rapidly following the injection of epinephrine. He was then started on injections of histamine in a dilution of 1:5,000,000. He was finally worked up to a dose of 1.00 cc. which appeared to be the maximum he could tolerate. Tablets of Catakon-A (National Drug Company—Phenergan 5 mg. d-Catechin 250 mg.), one four times a day, also helped about as much as the histamine injections. As might be expected, when the histamine injections and the Catakon-A were given together they appeared to neutralize each other. Pyribenzamine gave no significant relief.

After a time it was established that Catakon-A gave him about three hours relief, regardless of the weather, and the histamine would protect him for about four hours unless the temperature was above 32° F. (0° C.) when it would protect him all day.

ACTH appeared to help for a time but he began to suffer from local reactions, depression and a sense of fatigue following this, which latter symptoms were also experienced with cortisone. He also reacted abnormally at times to these drugs with fever. Ascorbic acid in doses of 200 mg. a day gave no significant help.

Between the Catakon-A and the histamine treatments the boy

TABLE XXII
HISTAMINE TREATMENTS

Injectons are to be given twice a day until relief is obtained or signs of histamine intoxication occur.

If relief is obtained the number of injections is gradually decreased as follows (assuming that relief persists). The same dose (i.e., same amount as that which gave relief) is continued:

One injection a day
One injection every other day
One injection every third day

Etc., until a maximum interval of two weeks is reached.

Treatments should then be continued until the patient is free from symptoms for six months. Then treatments may be discontinued.

Dosage as follows: Give same dose twice a day				
<i>Day</i>	<i>Date</i>	<i>Histamine</i>	<i>Amount</i>	<i>Remarks</i>
1		1/10,000	0.10	
2			0.15	
3			0.20	
4			0.25	
5			0.30	
6			0.35	
7			0.40	
8			0.45	
9		1/5,000	0.25	
10			0.30	
11			0.35	
12			0.40	
13			0.45	
14		1/1,000	0.10	
15			0.15	
16			0.20	
17			0.25	
18			0.30	
19			0.35	
20			0.40	
21			0.45	
22			0.50	

If this dose is reached without benefit please report to Dr. Glaser.

SIGNS OF HISTAMINE INTOXICATION

When these appear the dosage must be reduced or kept at the same level until symptoms disappear when an attempt to increase the dose is made:

Headaches
Dizziness
Abnormal warmth
Nausea
Vomiting
Faintness
Precipitation of acute attack of asthma

Symptoms of histamine intoxication may be controlled by a dose of epinephrine.

did reasonably well. Sometime afterwards the family moved to another city and the mother wrote a year later that the boy was having considerable difficulty. Because of the publication of Steinhardt and Fisher (17) it was suggested that he be studied from the standpoint of cryoglobulinemia and it is to be hoped that this will be done and the patient again reported upon later. However, the best hope for this boy at the moment would appear to be removal to a tropical climate.

The etiology of this condition is unknown. Rinkel (15) believes that an underlying food allergy is an important cause. The case of Kaufman (10) described above lends significant support to this observation. Rinkel also states that this condition, which he terms thermal allergy, may be produced by any type of inhalant but that house dust is an important cause.

TREATMENT OF ALLERGY TO COLD

This is illustrated in the case report of my own patient recorded above. If Rinkel (15) is correct, an underlying allergy to food or an inhalant should be sought and treated. The orthodox treatments are by means of gradually accustoming the patient to increasingly colder temperatures and the injection of histamine. Antihistaminics appear to give relief in some cases reported in adults. Further experience with ACTH and cortisone is highly desirable.

Allergy to cold, although presumably rare, is an important condition from the practical standpoint, as was indicated long ago by an editorial in the *Journal of the American Medical Association* (7). This stated that there are two important considerations in this respect: Persons who are sensitive to cold risk their lives by bathing in cold water. Also, in efforts to determine the exact mode of death in cold water, the possibility of death from the direct or indirect effects of cold allergy should not be overlooked.

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EOSINOPHILIC PNEUMONOPATHY

(Löffler's Syndrome; Tropical Eosinophilia)

THERE is a group of diseases, the nature of which is not entirely clear, characteristically accompanied by eosinophilia. At least two of the better known of these affect the lungs and are of particular interest to the allergist because of possible allergic origin. These are the so-called "Löffler's syndrome" and "tropical eosinophilia." Because the relationship between these two diseases is not completely clear and because other pulmonary diseases occur which have certain similarities to each of these, but cannot be classified as either, the term "eosinophilic pneumonopathy" was introduced by Apley and Grant (1) in 1944. Until more knowledge is available it would seem that this term is highly appropriate. Associated with this syndrome and of particular interest to the pediatrician are the disseminated visceral lesions accompanied by eosinophilia described by Zuelzer and Apt (15), in which, along with many other abnormalities, pulmonary infiltrations and asthmatic complaints may occur. For a review of the other numerous conditions, including periarteritis nodosa, which might be discussed under the term "eosinophilic pneumonopathy syndrome" reference is made to the communication of Ensign (5).

LÖFFLER'S SYNDROME

Löffler (8, 9), in 1932 and again in 1936, reported a new clinical syndrome commonly characterized by eosinophilia in the peripheral blood accompanied roentgenographically by a succession of transient pulmonary shadows of varying character which may resemble tuberculosis or bronchopneumonia but usually do not remain in one spot for more than two weeks. As one shadow disappears more shadows may appear. The duration is commonly several weeks. In 1945, Miller (10) reported a case of Löffler's syndrome in this country and could find the records of only four other case reports

in the American literature. However, since then there have been numerous case reports but few in infants and children.

Ham and Zimdahl (6) listed five principal diagnostic points in this disease: (1) pulmonary infiltrations which may be unilateral or bilateral and vary greatly in size, number and location; (2) fleeting and changing character of the infiltrations; (3) blood eosinophilia. This may be only slightly elevated (10 to 15 per cent) or may be as high as 60 per cent with or without an associated leukocytosis. There is no relationship between the degree of the eosinophilia and the intensity or size of the infiltration; (4) the patients may have only very mild symptoms or none at all and the disease be suspected only after taking a routine chest film or making a blood count. Symptoms, if present, usually consist of a slight elevation of temperature, mild cough, usually without sputum and general malaise. Upon physical examination occasional moist rales may be heard over the lung fields, and (5) short duration of signs and symptoms. The duration of the disease is quite variable. The incidence in males is greater than in females and more cases occur in July and August than any other time of the year.

In the differential diagnosis of Löffler's syndrome all other causes of blood eosinophilia must be ruled out, and it is also important to rule out tuberculosis. The syndrome is commonly believed to be of allergic origin, the interstitial tissue of the lungs being the shock tissue involved. The factors favoring the allergic hypothesis as summarized by Clark and Rosenberg (3) are: The transient character of the pulmonary lesions; minimal disturbance of health with extensive pulmonary lesions; blood and sputal eosinophilia and absence or minimal signs of infection, as fever, increased sedimentation rate, commonly no leukocytosis and no signs of systemic intoxication. There is a past history of allergy or associated allergies in over half of the cases.

One relatively common cause of this disease appears to be an allergic reaction to parasitic infection. Scheer (12) reviewed all the cases of children admitted to the pediatric ward at the Metropolitan Hospital, New York City, with such infections for a two-year period from May, 1949, to May, 1951. They ranged in age from two and one-half to eleven years. Of the thirty-five cases reviewed,

at least three could be considered in retrospect to have had Löffler's syndrome and an additional three cases were questionable.

O'Byrne (11) described a case of Löffler's syndrome in a five months old girl who was first seen because of gastrointestinal allergy. Both parents were allergic. The child was sensitive to various foods, particularly cow's milk, and orange juice. At the age of seven months she was hospitalized because of fever of 38.3 C. (101 F.), mild diarrhea, and fairly severe anemia. Roentgenograms showed what appeared to be a rather widespread bilateral bronchial pneumonia. This changed in position and intensity over a period of ten weeks and at no time were physical signs present in the lungs. She had a severe anemia on admission with a red blood cell count of 1.9. The white blood cell count varied between 1,700 and 7,600; neutrophils 10 per cent to 76 per cent, and eosinophils 8 per cent to 50 per cent.

Clinically the patient was apathetic, moderately dyspneic and at times slightly cyanotic. Response to sulfonamides was unsatisfactory and antibiotic drugs were not then available. It was three weeks before her temperature became normal. Laboratory studies, except as indicated above, were completely negative including examination of the stools for parasites. Sternal puncture showed normal marrow. The child did well on soy bean milk and gradually overcame her allergy and the pulmonary signs disappeared.

Shecter and Graub (13) described Löffler's syndrome, the origin of which could not be determined, in each of two year-old twins, a boy and a girl. Clark and Rosenberg (3) described a case in a four-year-old boy with ascaris infestation which cleared when this was eliminated. They pointed out that the Swiss observers have emphasized the rather frequent association of the syndrome with ascaris infestation.

At present there is no specific treatment for Löffler's syndrome except to remove the offending allergens, such as those of parasitic origin if they can be found. However, cortisone and corticotropin (ACTH) are highly effective as symptomatic remedies (5).

TROPICAL EOSINOPHILIA

This disease, which was first described by Weingarten (14) in 1933, is of great importance in India, and may possibly occur else-

where. According to Hodes and Wood (7) the diagnosis is not difficult if the possibility of its occurrence is kept in mind. The typical clinical picture consists of a pronounced eosinophilic leukocytosis in a patient with asthmatic bronchitis, fever, a palpable spleen, and roentgen evidence of diffuse mottling and "soft" nodulation throughout both lungs. The etiology is unknown but the asthmatic manifestations and the eosinophilia suggest an allergic factor, perhaps in response to parasitic allergens. There is no seasonal incidence and race and age are not factors. De Zoysa (4) mentioned three cases in children four, five, and twelve years of age respectively and Hodes and Wood (7) in a seven-year-old. However, most of the cases have been reported in adults.

Tropical eosinophilia characteristically responds to treatment with arsenicals, particularly intravenous neoarsphenamine. Without arsenical therapy the condition tends to persist. It would be interesting, in view of the close resemblance of this disease to Löffler's syndrome, to see if tropical eosinophilia would respond to cortisone or corticotropin (ACTH), and if Löffler's syndrome would respond to arsenicals. Definitive experiments in this direction have not yet been published but should this occur a differential diagnosis in the light of our present knowledge would be all but impossible.

Cartwright (2), in his review of these diseases, stated that "actually there are differences only in degree and it is debatable whether tropical eosinophilia and Löffler's syndrome are different diseases." De Zoysa (4) also expressed his opinion to the effect that Löffler's syndrome, tropical eosinophilia, and periarteritis nodosa are but different manifestations of a single pathological process which has as its basis sensitization of blood vessels and that these three diseases are merely gradations of hyperergic vascular response.

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THE ALLERGIC TENSION-FATIGUE SYNDROME

THE CHILD who is listless and restless is a common problem in pediatric practice. Schneider (4) has applied the term, "hyperkinetic child" to restless, overactive, distractable children whose behavior includes inattention, flightiness of ideas, an explosiveness of motor output, and those whose behavior in the school, home and doctors' examining rooms includes unpredictable impulsive behavior. The diagnostic possibilities which one must consider in dealing with such children are practically limitless. The subject has recently been reviewed by Speer (6) who used the term, "the allergic tension-fatigue syndrome" to describe those cases in which there is an allergic etiology. Speer pointed out that as long ago as 1916, Hoobler (1) called attention to a group of allergic children as "restless, fretful, and sleepless," and who were referred to him with those complaints. More important contributions were made later by Shannon (5), in 1922, who published what was perhaps the first report recognizing that nervous disturbances could at times constitute a primary allergic syndrome. Kahn (2), in 1927, first described pollen toxemia in children and noted that languidness and restlessness were the rule, alternating with spells of intense temper and fury. Still others, as documented by Speer, have further added to our knowledge of this subject.

Speer stated that fatigue of allergic origin tends to take two forms; in one the child is sluggish or lethargic, has great difficulty in awakening from sleep, is torpid afterwards and this state of affairs may interfere with his progress in learning. The condition may be much worse if it is accompanied by oversensitiveness and ill temper. In the second type of allergic fatigue the child is tired rather than sluggish and may come in from play to lie down. According to Randolph (3) this symptom is characteristically not improved or is even made worse by rest.

Ancillary symptoms accompanying the allergic tension-fatigue syndrome may be, according to Speer, vague aching, particularly of the legs, which probably represents a severe form of fatigue, hyperhydrosis; pallor and infraorbital edema and, of course, the more frank evidences of allergy as eczema, pollinosis, asthma and other manifestations. In the differential diagnosis one must particularly consider disorders of the central nervous system; borderline deficiencies of nutrition, particularly iron deficient anemia; endocrine disorders, particularly mild degrees of hypothyroidism; and subacute and chronic infections, particularly rheumatic fever. There are, also, many other disorders which can produce this symptom. However, one may be lead to suspect that the syndrome is of allergic origin if it occurs in a child known to be allergic or in an allergic family and, particularly, if no other explanation is forthcoming. In most of these cases foods are primarily at fault and, as is usually the case, major foods such as egg, wheat, and milk. Pollen, however, as mentioned above, may also produce this syndrome, and I have had the opportunity of studying one boy with a severe behavior problem due to allergy to cold (see Chap. 54).

The following report of one of Speer's patients illustrates some of the more important findings in a rather typical case.

This was a boy whose early infancy was uneventful. At the age of twelve months he began to be restless and seemed unable to relax enough to take naps. About the same time his stools began to be hard, and he was "gassy." He was no longer happy, but had become whiny and cross. His mother had noted a gradual increase in milk intake and a corresponding drop in appetite for solids. He had always tended to perspire easily, and in recent months this had become much more severe. At this time the physical examination was negative. The combination of tension, insomnia and constipation with increased milk intake threw suspicion on that food. The child was put on a soybean milk (Mull-Soy), and milk products were removed from the diet. This maneuver was followed by prompt improvement in the child's behavior. He was sleeping all night by the third night and was again happy and calm. His appetite improved greatly, and his stools became normal. A return to milk one week later slowly brought about a return of nervous and gastrointestinal difficulties. Several attempts to go back to milk have produced the same result.

The child remained well until the age of three years. About this time his disposition underwent a gradual change. His usually sunny disposition disappeared, and he became increasingly hard to manage. Investigation of his environment failed to show faults in parent-child relations. Physical findings were negative except for infraorbital edema. His parents had noticed this, but thought it was nothing more than a facial trait peculiar to him. Although there was no real evidence that allergy was again the cause of his tense behavior, the parents agreed to proceed with allergic study. Skin tests demonstrated no definite reactions. His mother suspected that eggs upset his stomach, but elimination of this food brought about no improvement. Wheat also was negative on clinical elimination, but elimination of corn coincided with marked relief in his restlessness and irritability. On the return of corn the child had one of his worst days. He seemed unusually wild and had difficulty in going to sleep that night. Corn was withheld for a second time with the identical reaction.

In the past three years his parents have learned a great deal. Various friends and relatives have taken it upon themselves from time to time to experiment with his diet. It is now obvious to all that milk and corn actually must be kept from him. It has also been learned that his intolerance to corn is absolute, while his sensitivity to milk is considerably less severe. He invariably reacts to corn and popcorn, but if he has milk no oftener than twice weekly there is no apparent difficulty. His mother has been encouraged to rotate his diet so as to avoid new sensitization.

Experience with this little boy over a six-year period clearly demonstrated that nervous manifestations of allergy are not necessarily dependant upon other allergic diseases.

Speer concluded his discussion of this problem with the statement that one must consider allergy as a possible factor in a child who is restless, languid and vaguely ill, or presents evidence of hyperkinesia without evidence of clear cut disease. Although the allergic tension-fatigue syndrome commonly occurs in combination with other allergic conditions, it often occurs alone and may properly be considered a primary allergic syndrome.

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CHAPTER 57

MISCELLANEOUS CONDITIONS OF INTEREST TO THE PEDIATRIC ALLERGIST

FAVISM

FAVISM may be defined as a disease due to allergy to the fava bean (*Vicia fava*) characterized by an acute hemolytic anemia accompanied by fever and malaise with hemoglobinuria and jaundice. Most of our knowledge of this disease is due to Luisada (6) from whom this brief description quotes freely. This vegetable is also known as the Italian bean, broad bean, and horse bean. It resembles the lima bean but is about twice its size. The bean may be eaten raw but is usually served with other vegetables.

Favism was known in antiquity and Luisada stated that it used to have a wide distribution in the Mediterranean basin. It now occurs particularly in Sardinia where many thousands of cases occur yearly in a population of one million. Besides the entire Mediterranean basin, cases have been reported in the United States and in England, chiefly, but not always, in patients of Mediterranean descent. The disease has a hereditary tendency with a familial incidence of about 20 per cent.

Favism may result from inhalation of the pollen of the bean but less frequently than from its ingestion. Fortunately the pollen is heavy and sticky and does not travel far from its site of formation. Favism is particularly prevalent in April and May when the plant is flowering and in June and July when the mature bean is marketed and eaten. The disease has been contracted by drinking the milk of a goat fed with fava beans, not a normal constituent of a goat's diet. In this connection it is interesting that nursing infants are not immune if the mother or wet nurse includes fava beans in her diet (6).

Larkin (4), who in 1952 reported a case in a one-year-old girl, stated that up to then nine cases had been reported in the American literature of which six were in children. Eight were in males who are most commonly affected. The disease tends to be more prevalent and more severe in children than in adults and almost all deaths from favism occur in children. The mortality is about 8 per cent (8). Diggle (2) has quoted Cadeddu to the effect that the findings in eight necropsies were those expected in any fatal hemolytic anemia, whatever the cause.

The amount of fava beans ingested bears little relation to the severity of the disease. Luisada has seen favism develop in a five-year-old child after eating a single bean. He also found that many of the patients tested show skin sensitivity to fava bean extracts.

The onset of the attack may be sudden. Symptoms may develop in a few seconds to hours when the pollen is inhaled; in five to twenty-four hours when the bean is eaten. Jacobs (3) states that the first symptoms may be dizziness, followed by vomiting, diarrhea, and complete prostration. Hemoglobinuria appears within twenty-four hours, the urine becoming red-brown to black in color. In Luisada's experience the patient usually dies if the acute hemolytic process with hemoglobinuria lasts more than three days. Chills and fever may be present. Jaundice appears within a few hours and may be accompanied by enlargement of the liver and spleen. An anemia of one million or less may develop with anisocytosis, poikilocytosis, polychromatophilia, and erythroblastosis. The hemoglobin may fall to as low as 10 per cent. A prompt reticulocyte response is noted in those patients that do not succumb within the first day or two. This is, however, a description of a severe attack. It must be remembered that milder attacks occur, the symptoms of which are much less marked. With subsequent attacks Luisada found that some type of immunity was likely gradually to develop.

The treatment is supportive with transfusion as indicated. According to Diggle (2), Leone obtained symptomatic relief with antihistamines. Cortisone or ACTH would appear to be ideal medications to try in this condition and Becker (1) appears to be the first to have reported such a case. This was a two-year-old boy of Italian extraction who was given 10 mg. of cortisone every six hours for four doses; then 10 mg. every eight hours for three doses;

then 10 mg. every twelve hours for two doses, and a final dose of 10 mg. one day later. The urine began to clear the day after the institution of cortisone therapy and was clear twenty-four hours later. The boy made an uneventful recovery.

In the differential diagnosis must be considered blackwater fever, Weil's disease, Lederer's anemia, catarrhal jaundice, and infectious hepatitis. Lecks (5) has made the highly practical comment that the sudden onset of asymptomatic jaundice in an Italian child should necessitate careful questioning for a recent history of fava bean ingestion.

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ALLERGIC ARTHRITIS

Rheumatoid arthritis and its possible relationship to bacterial allergy will be discussed subsequently (see Chap. 58). Bacterial allergy of other forms involving joints has been discussed by others since the early publication of Freiberg and Dorst (4) and will not be further considered here. Arthritis as part of the clinical picture of serum sickness and arthritis as a result of drug allergy, particularly penicillin, are well known. Less familiar are the articular manifestations of anaphylactoid purpura (Schönlein-Henoch syndrome—see Chap. 49). The literature also contains numerous scattered reports of arthritis due to allergy to various foods and occasionally accompanied by angioedema and or urticaria. Reactions of this latter type are not particularly common and few cases have been reported in children. No attempt has been made to make a thorough search of the literature and only the two following cases are briefly noted to illustrate this condition.

Lewin and Taub (5) reported the case of a sixteen-year-old boy

who had suffered from intermittent stiffness and swelling of various joints since the age of six years, sometimes as often as every two or three months. These attacks were shown to be due to the eating of English walnuts and on removal from the diet the symptoms disappeared.

Criep (1) recorded a twelve-year-old girl with recurrent arthritis involving particularly the right ankle and the left wrist. She had never had fever accompanying the arthritis, the sedimentation rate was normal and the blood showed an eosinophilia of 10 per cent. She was known to have an intolerance for egg which produced urticaria and only on one occasion swelling of her right ankle. On skin testing she gave a very strong reaction to egg and on removal of egg from her diet she remained free from arthritis during an observation period of two years.

TRANSIENT SYNOVITIS OF THE HIP JOINT

Transient synovitis of the hip joint is a term used to denote a not infrequent condition in which a child becomes disabled as a result of what appears to be a synovitis of the hip. The condition is important because it must be distinguished from more serious diseases as tuberculosis, pyogenic arthritis, osteomyelitis, and aseptic bone necrosis (Legg-Perthe's disease). The literature on this subject has been reviewed by Edwards (2). The etiology of the condition is unknown. Some believe it to be due to a nonspecific infection or to a focus of an infection. Allergy has also been suspected as a possible cause. Children below the age of ten years are primarily affected and in twenty-two cases studied by Finder (3) the average age was 5.4 years. Girls as well as boys are affected. The onset may be insidious or acute and symptoms may last from one day to several weeks.

According to Edwards the most common symptoms are pain and limping. Clinically there is demonstrable spasm in all muscles about the hip. The child holds the leg in the position of comfort, or flexation and adduction. A low grade temperature may be present varying from 37.2 C. to 38.3 C. (99 F. to 101 F.), rarely going as high as 39.4 C. (103 F.). The laboratory examinations give no significant help. Pathological sections of the synovial membrane have never been studied. Edwards aspirated the hip joint on two occasions

finding xanthochromatic bacteria-free fluid which clotted readily. He did not mention staining the sediment for eosinophils. Edwards feels that the most likely etiology is allergic hypersensitivity or a toxic reaction to a focus of infection. Two of his patients with a history of allergy recovered dramatically in one day and remained well following treatment with tripeleminamine (Pyribenzamine) which he feels lends support to the theory that the condition has an allergic or hypersensitive basis.

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GENITOURINARY ALLERGY

Under this subject one might consider vulvovaginitis due to pollen and hematuria as a complication of anaphylactoid purpura. These conditions have been discussed previously (see Chaps. 42 and 49). Other than these manifestations little has been written on possible genitourinary allergic manifestations and practically all of this, except enuresis, to be discussed subsequently, has been with reference to adults. Duke (3) has reported food allergy as a cause of bladder pain and Robinson (4) uterine spasm caused by orris root. Abortion caused by spasm of the uterine muscle as part of a generalized reaction to allergens is quite well known.

Dees and Simmons (2) made a study of 613 patients with six urological conditions selected for analysis because the symptoms reported could have been compatible with an allergic reaction and the etiology was unknown or not fully explained. They found allergic manifestations present in 12 per cent of the entire group. This is so similar to the accepted percentage of allergy in the general population that they did not feel justified in suspecting that allergy plays any major role in these disorders. In none of the cases which

were studied completely urologically and for allergy did the allergy seem to be of etiological significance.

ENURESIS OF ALLERGIC ORIGIN

According to Bray (1) enuresis may accompany allergic disease as a result of the underlying allergy or may be the sole manifestation of allergic disease. In a thousand allergic children he found that about 5 per cent over the age of seven years suffered from some degree of enuresis.

A comparison of the nerve supply of the lungs and the bladder gives a possible reason for such an association. The parasympathetic nervous system supplies both the constrictor fibers of the bronchi and the motor nerves to the detrusor muscle of the bladder and inhibitory fibers to the internal vesicle sphincter. On the contrary the bronchi are dilated by sympathetic fibers inhibiting their smooth muscle. Sympathetic fibers also stimulate the detrusor muscle of the bladder and the internal vesicle sphincter. Obviously stimulation of the parasympathetic system may lead to bronchospasm, or to the discharge of urine or both according to the location or intensity of the stimulus. Thus, any endeavor to stimulate the sympathetic to counteract the asthmatic tendency may lead in addition to cessation of the bed wetting habit.

The analogy between enuresis and allergic conditions in general does not end with the similarity in innervation of the affected organs. Both conditions tend to occur periodically; both tend to be worse at night; both are accentuated by fatigue or worry; in both there is sympathetic exhaustion; and both commonly clear up on admission to the hospital.

In fifteen cases of enuresis where this was the sole complaint, Bray found that three were cured by eliminating substances giving positive skin reactions.

Clinically I had observed that occasionally old men with asthma suffered acute retention following the use of ephedrine. Acting on this observation and Bray's suggestions I have used a mixture of ephedrine, atropin, and phenobarbital along with other hygienic measures in the treatment of the usual non-allergic types of enuresis. Occasionally this seems to have met with success. However,

from a practical standpoint, a relationship between allergy and enuresis does not appear to have been convincingly established.

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ALLERGIC PAROTITIS

The reviews of Waldbott and Shea (2) and of Swinney (1) give very good evidence of the existence of recurrent swellings of the parotid gland which are due to allergy. A few cases have been reported in children. Swinney states that there is usually a history of allergy, either familial or personal; there are recurrent attacks of unilateral or bilateral swelling of the parotids; the saliva is thick and ropy and often forms plugs or casts of the duct and contains many eosinophils. Attacks are precipitated by specific allergens, inhalant or ingestant, and are relieved and prevented by avoidance or hypsensitization.

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APHTHOUS (ULCERATIVE) STOMATITIS

Aphthous (ulcerative) stomatitis, colloquially known as "canker sores," is a condition which occurs not infrequently during the course of acute infections at any age but may occur without evident cause at any time, may occasionally be recurrent, and is often very painful. The word "aphthous" is derived from the Greek and means "ulcerous"; the word "canker" is derived from the Latin word "cancer," meaning "crab," but in this sense has no reference to the malignant disease, cancer, although the term has the same derivation.

Dodd and Ruchman (3) describe aphthous stomatitis as consisting

of shallow ulcers surrounded by a red areola and covered with a false membrane. The ulcerations occur on the inner surfaces of the lips, the buccal mucous membranes, and, more rarely, at the gingivo-dental margin or on the palate and the tongue, especially at the edges and tip. One particular form, which runs a typical clinical course characterized by fever, sore throat and other symptoms and may at times be almost epidemic in children, is known as "herpangina" and is due to the Coxsackie virus. The virus of herpes simplex may be the etiological factor in some cases of aphthous stomatitis but the popular belief that this is the most common cause is incorrect as indicated by the work of Blank and associates (2) and Dodd and Ruchman (3).

Besides infection, aphthous stomatitis may be due to trauma or to food or drug allergy, in which case the mechanism of the allergic reaction is not known. Aphthous stomatitis of allergic origin is rare in children but its occurrence in adults, though not frequent, is part of the experience of every internist and allergist. The patient has nearly always learned from experience which food or foods cause the stomatitis. In the few adults seen in consultation, these have been milk, chocolate, nuts, and berries. Skin tests have been negative. Elimination diets have been of no assistance although these, as well as provocative feeding tests, might well be of help in a large series of cases.

The symptomatic treatment of aphthous stomatitis is not very satisfactory. Some relief may be obtained by the use of anesthetic lozenges. Occasionally a powdered aspirin tablet held against the ulcer produces satisfactory temporary analgesia and some patients obtain such relief by holding one or two teaspoons of an elixir of an antihistaminic, particularly Benadryl or Pyribenzamine, in the mouth, as the antihistamines have a local anesthetic action. One adult patient found that Campho-Phenique* applied locally on a cotton-tipped applicator gave her the best symptomatic relief. Hydrocortisone ointment (dental) has been described as helpful by Bergman (1). It is applied every two hours and may require twelve hours or more to achieve an effect. One thirteen-year-old girl with severe recurrent attacks of unknown origin found that this prepara-

* Manufactured by the Sterling Drug Co. Said to contain phenol and camphor in an aromatic solution.

tion irritated during the acute stage but gave some relief after the acute inflammation had subsided.

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BRONCHIECTASIS

Irreversible bronchiectasis, although rarely occurring in asthmatic children, according to Chobot (1) and verified by my own experience and also believed to be rare in adults with asthma by Waldbott and associates (5), is nevertheless an important disease to the pediatric allergist. It is important because of the asthmatic symptoms which occur in about a third of the cases (2). Bronchiectasis in childhood has been most thoroughly studied by Field (2, 3, 4) who stated that in about a fifth of the cases the onset was in the first year of life and in over half of the children (55.6 per cent) the parental history associated the onset with an attack of pneumonia or pertussis. Bronchiectasis probably originates so frequently in early childhood because of the relatively small size of a child's bronchus which renders it more easily obstructed, and the child is more susceptible to predisposing respiratory diseases (3). In this connection Field (3) made the highly practical point that if a cough continues for six weeks or longer after the initial acute illness, full investigations should be carried out and all possible means of treatment instituted.

The characteristic features of the disease include a constant cough with or without sputum, as the sputum is often swallowed by children. Hemoptysis is rare, and clubbing of the finger tips, almost never seen in bronchial asthma in children in my experience, was found by Field (2, 3, 4) to be present in almost half of the cases and when present was diagnostic of irreversible bronchiectasis.

The relationship of allergy to bronchiectasis does not appear to be very definite. According to Field (3), non-aeration of alveoli is a feature common to the childhood illnesses predisposing to bronchiectasis and is regarded as the important factor in the etiology of

the disease, infection playing a subsidiary part. It would, therefore, appear that since allergic manifestations involving the lung may, because of the associated edema, cause non-aeration of the alveoli with subsequent collapse and infection, that allergy might be an important cause of this disease. In ninety-nine cases classified by Field as doubtful bronchiectasis when first seen, almost half (47.5 per cent) suffered from asthma. However, in the cases complicated by asthma which were subjected to radical removal (4) of the diseased tissue, over half were classified as cured. This could be looked upon as analogous to removing a focus of infection and thus relieving a bacterial allergy or as relief of symptoms resembling asthma due to mechanical factors present in the diseased tissue. The latter seems unlikely as in that case the asthma would, in some instances, certainly be localized to one lung, or a segment of a lung, which does not happen. It would, therefore, appear theoretically possible that although bronchiectasis may secondarily result as a complication of asthma, it is much more likely that asthma results from the bronchiectasis and is of bacterial origin. There is, however, no reason why bronchiectasis and bronchial asthma of different etiology could not co-exist in the same patient though studies of such cases are lacking. From the practical standpoint, bronchiectasis is not a significant problem numerically to the pediatric allergist. I not infrequently study patients referred because of bronchiectasis and asthma but these have, thus far, invariably turned out to be bronchial asthma alone or a form of the so-called "reversible" bronchiectasis in which a physician often, with the assistance of a good imagination, can see tubular dilatation of the bronchi which may be secondary to asthma and which responds to antiasthmatic therapy.

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KARTAGENER'S SYNDROME

Kartagener's syndrome, a triad of situs inversus, bronchiectasis, and chronic sinusitis, was first reported in 1933 (5). Bergstrom and associates (1) stated that up to the time of their publication in 1950, eighty cases had been reported. The disease is of interest to the allergist because these individuals may wheeze and may be suspected of suffering from bronchial asthma or perennial allergic rhinitis. It is of interest to the pediatrician because in 90 per cent of the cases in which details as to the age of onset of symptoms were given, these began at fourteen years of age or less and in over half of these under two years of age (1). At times these patients may be suspected of suffering from mucoviscidosis.

Bronchiectasis occurs with much greater frequency in individuals with situs inversus than in the general population, the reviews indicating an incidence of 12 to 23 per cent (1). The situs inversus need not be complete. Olsen (7) observed fourteen cases (16.5 per cent) in eighty-five patients with dextrocardia at the Mayo Clinic during a twenty-seven-year period, and ten of the fourteen had nasal polypsis. Dickey (3) has suggested that from his study of Kartagener's syndrome it may be concluded that a congenital factor of some sort plays a part in the pulmonary features of the disease. Whether there is a developmental error in the bronchial walls or whether the pulmonary lesions are secondary to the cardiovascular anomalies is still open to debate. In any case it is probable that in most instances atelectasis precedes bronchiectasis. The possibility has also been pointed out (1) that the relationship between bronchiectasis and dextrocardia may be a mechanical one, i.e., the position of the great vessels may interfere with proper mechanical drainage. It should be noted, however, that stillborn or newborn infants with dextrocardia do not have pathological changes suggestive of bronchiectasis (4). In this connection, Conway (2) has made the interesting observation that in the published reports on Kartagener's syndrome, bronchiectasis is usually noted as being of the tubular or "varicose" instead of the cystic variety usually regarded as congenital.

Dickey (3) described five cases in children, four girls and one boy, six weeks, four, nine, ten, and fourteen years of age respectively. All of the children had a history of nasal difficulty and cough since early infancy and in the case of the nine-year-old girl, mu-

coviscidosis had been considered. The fourteen-year-old boy had what was described as an asthmatic attack at five months of age and attacks had recurred ever since then. He had been studied from the standpoint of allergy without benefit. Four of Dickey's patients had complete situs inversus; one had dextrocardia only. The ten-year-old girl came to necropsy and was found to have other anomalies of the heart. Three of the children who had lobar resections showed considerable improvement of their pulmonary symptoms.

I have encountered but one case of this syndrome, a woman seen in consultation because of asthma. I now have, however, under my care an infant in a highly allergic family who has a partial dextrocardia who may possibly develop this syndrome. Since early infancy he has had repeated respiratory infections. Because of the family history of allergy and the dextrocardia, these infections have been treated with more than ordinary vigor and other prophylactic measures have been instituted in an attempt to prevent the development of bronchiectasis and asthma.

Bergstrom and associates (1) reported a family in which there occurred two cases of Kartagener's triad and two of bronchiectasis without situs inversus in six siblings. They also reviewed three other family groups who had shown multiple occurrences of Kartagener's syndrome. Katz and associates (6) stated that Kartagener's triad presents several practical considerations. Persons with situs inversus, especially with concomitant sinus infections, should be thoroughly investigated for bronchiectasis. The examination should include bronchography. The families of patients with Kartagener's syndrome should be screened for similar anomalies.

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ISOLATED MYOCARDITIS

Saphir (3) states that Fiedler's or isolated myocarditis is a special form of myocarditis although it is not specific in the anatomic sense. This term denotes more or less diffuse inflammatory changes in the myocardium of wide variety and varied etiology; the principal thing that they have in common is isolated involvement of the myocardium by a nonspecific lesion, without inflammatory changes in the endo- and pericardium. The disease does not vary in histologic details from the myocarditis which is occasionally encountered in the course of acute infectious disease. Clinically the symptoms are those of progressive myocardial failure; a weak, rapid pulse, low arterial pressure, an increase in the area of cardiac dullness and sometimes precordial pain. The patients often die suddenly and the myocarditis is commonly not diagnosed except at necropsy.

The literature of isolated myocarditis has been reviewed by Lipman (1) who states that about 100 cases have been recorded in infants and children. The etiology is completely unknown. Rosenbaum and associates (2) were unable to confirm that drug sensitivity might be an etiological factor. Lipman believes that the disease is probably of allergic origin and reported a case with recovery in a twenty month old girl in whom he felt that sensitivity to penicillin might have caused some of the myocardial damage. It is interesting that this patient a year later developed ragweed pollinosis.* Further elucidation of the possible role of allergy in this disease is greatly to be desired.

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* Personal communication from Dr. Lipman.

THE COLLAGEN DISEASES

WHETHER or not the so-called "collagen diseases" should be considered in a book of this character is debatable, particularly since they play such a minor role in diseases of children in general and an even more insignificant role in the practice of the pediatric allergist. However, since a knowledge of these diseases has been recommended for those who wish to apply for certification in the specialty of allergy, in line with attempts to raise the standards of training in allergy, it has been thought advisable to include here a very brief discussion of these conditions.

All these diseases have in common an obscure etiology and a pathology characterized by damage to collagen fibers and the ground substance of connective tissue. Klemperer (1) has stated as follows: "The term 'collagen disease' was originally proposed to call attention to systemic alterations of the extracellular components of the connective tissue as a pathologic-anatomic feature common to a group of apparently heterogenous diseases. It was not intended to use the term in a diagnostic sense since it was realized that it referred to one morphologic characteristic only and, therefore, obviously could not define the underlying morbid processes of the diseases grouped together." The term usually includes rheumatic fever, rheumatoid arthritis, polyarteritis (periarteritis nodosa), lupus erythematosus, progressive systemic sclerosis (scleroderma), and dermatomyositis. With respect to this, the statement of the Committee of the American Rheumatism Association (4) should be kept in mind, "Within this group of diseases, however, there are occasional patients in whom several clinical patterns are merged to the extent that a definite diagnosis is impossible. These conditions have been called 'undifferentiated collagen disease.' In some patients a diagnosis may be established by continued observation; in others only at post-mortem examination, and in a few a final diagnosis cannot be reached even after a careful and complete autopsy."

Klinge (2), because of similar changes in hypersensitive animals, came to the conclusion that the tissue damage in human rheumatic disease was also due to hypersensitivity and, therefore, included rheumatic fever. Middleton's (3) review, however, has brought up to date the evidence that the characteristic changes of collagen disease may occur independently of any evidence of sensitivity. It therefore seems illogical for the allergist to consider these diseases his particular province, even though the advent of adreno-corticotrophic hormone and cortisone which he uses so much has had such a marked influence upon the treatment of some of the collagen diseases.

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RHEUMATIC FEVER

Rheumatic fever is such an important disease in pediatric practice and is so thoroughly presented in pediatric textbooks that any detailed consideration here would be utterly superfluous except, perhaps, as it may or may not be related to allergic diseases.

Young (2) made an analysis and comparison of the principal measurements, physical characteristics and relative bodily proportions in groups of boys and girls of different ages who were under treatment for asthma and rheumatic fever respectively at the Hospital for Sick Children on Great Ormond Street, London, and a group of normal children. He concluded that the differences in the three groups of children, the asthmatic, the rheumatic and the normal, in respect to the aggregate of physical characteristics studied, are relatively so slight that they cannot be considered to support the view that asthmatic and rheumatic children really differ on the average from one another or from the general population of children in bodily conformation or physical type. They may possibly, and indeed probably, differ in other constitutional traits.

Rittwagen, Romano, and Svigals (1) studied a group of 100 children with rheumatic fever ranging in age from five to fourteen

years, with an average age of ten years, with respect to the relative incidence of allergy in these children and a control group of non-rheumatic children. The incidence of allergic disease, either present or past, was three times as great in the rheumatic group. The incidence of allergic diseases in the families of the rheumatic patients was also much greater than that of the general population. What significance these findings may have with respect to the occurrence of rheumatic fever in childhood remains to be evaluated.

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RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a systemic disease characterized by a slowly progressing swelling and stiffness of the joints accompanied by pain and muscular atrophy. It is rare in children, occurring with less than 3 per cent of its frequency in adults (1). The disease may, however, start as early as fourteen months and girls are much more frequently affected than boys (2). In adults both hypertrophic and atrophic forms may occur. In children only the atrophic form is seen and this was first described in detail by Still (9) who pointed out that the same joint manifestations may be present as in the atrophic form in adults, but that in children these manifestations may be associated with generalized lymphadenopathy, splenomegaly, hepatomegaly, and sometimes adhesive pericarditis or other visceral diseases. This is popularly known as "Still's disease," but this term, according to Lockie and Norcross (4), should be discarded since it is the same disease as in adults modified because of the age of the patient.

The etiology of rheumatoid arthritis is unknown (5). An infectious origin is strongly suspected and there is evidence that in some way the hemolytic streptococcus may be associated with the disease since this organism is found in over 50 per cent of throat cultures (2). Focal infection may play a role but there is no good evidence to support this opinion. In jaundice, pregnancy, and after surgery and anesthesia there may be marked remissions suggesting a bio-

chemical factor (8). There is little evidence that rheumatoid arthritis has anything to do with the ordinary forms of allergic manifestations, as atopic dermatitis (eczema), pollinosis or asthma, but no detailed studies in this disease, such as those of Rittwagen *et al.* (7) with respect to rheumatic fever, have been made. Rackemann (6) stated that the relationship of arthritis to these particular forms of allergy is very doubtful. However, the presence of bacterial allergy, either to the organisms or their toxins, may possibly play a very important part in the etiology of this disease.

The pathological picture of the articular lesions varies greatly with the stage and severity of the disease. Proliferation of synovial cells with thickening of the synovial membrane occurs early. Later the cartilage is involved in a destructive process and this may be accompanied or followed by bony proliferation (5). The roentgenological changes most characteristic of this disease are: (1) decalcification; (2) bone destruction; (3) joint space narrowing, and (4) soft tissue changes (2). The subcutaneous nodules of rheumatoid arthritis, which are similar to the nodules of rheumatic fever, constitute the one characteristic pathological lesion of the disease (5). They are present in about 20 per cent of cases (2). There is usually anemia and the basal metabolic rate is commonly low. The sedimentation rate may be greatly increased.

Rheumatoid arthritis may start insidiously but may be preceded by a variety of symptoms, including loss of weight, a low grade fever and vague symptoms which may include nervousness, fatigue, sleeplessness, headache, anorexia, digestive disturbances, weakness and paresthesias of the fingers and toes (1). The disease commonly begins symmetrically in the joints of the hands and feet and gradually progresses towards the trunk. Emotional reactions occur early making the care of these children more difficult (1).

Early in the disease it may be monarticular and the temporomandibular joint may be the first to be affected. The mandibular center is probably the most active area in the growing jaw and maintains its activity longer than most of the other centers of the head, persisting until at least the twentieth year. If this center is disturbed, since it is critically important in jaw development, a localized cranio-facial dysplasia may occur. This is expressed as a rather typical failure of development of the lower jaw, which had been

noted by Still (9). This deformity, appropriately termed by the Germans "Vogelgeschicht," or "bird face," is not characteristic, but rheumatoid arthritis should be suspected whenever it occurs. Its incidence is between 14 and 17 per cent (3).

Rheumatoid arthritis has no apparent relationship to rheumatic fever but may at times be difficult to differentiate from this disease in the infrequent instances in which it occurs following bouts of rheumatic fever (1). Rheumatoid arthritis may occasionally be distinguished from rheumatic fever by its insidious onset, its chronic course, the absence of endocarditis, the absence of a striking response to salicylates, and the development of chronic deformity of the joints (1).

Coss and Boots (2) pointed out that the many similarities between rheumatoid arthritis and rheumatic fever lead to the interesting conjecture that the same kind of process may be responsible for both conditions, as an infection with the hemolytic streptococcus, the former being a much slower and much more insidious process. This theory, however, awaits confirmation.

Lockie and Norcross (4), in 1948, reported a series of twenty-eight cases of juvenile rheumatoid arthritis in children observed over a fourteen-year period. Since twelve cases (42.8 per cent) made a complete recovery, they felt that the older pessimistic prognosis is not justified.

Measures of proven value in the treatment of the disease are principally those directed towards improving the patient's health, particularly rest, improvement of the general nutritional state which includes treatment of commonly associated anemia and the removal of foci of infection, the correction and prevention of deformities, physiotherapy, and psychotherapy. Salicylates are useful for the relief of pain and sedatives should be used as necessary. Chrysotherapy may be of value, as may phenylbutazone. ACTH, cortisone, and hydrocortisone have not yet been thoroughly evaluated, but appear to be very helpful for symptomatic relief (5).

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POLYARTERITIS

(Periarteritis Nodosa)

Polyarteritis (periarteritis nodosa) is not a common disease. Dent *et al.* (6) reviewed the literature in 1953 and stated that less than 500 cases had been reported in adults and less than sixty among children. It occurs at almost any age. Wilmer (16) reported two infants who died at the ages of ten and thirty-seven days, respectively, in whom lesions typical of polyarteritis were found. Fager *et al.* (7) noted that the disease has been reported up to the age of eighty-nine years. In 484 cases reviewed by them, 90 per cent occurred after the age of fifteen years. The sex ratio was two males to one female in adults and equal in children. The highest incidence of the disease occurred in the fourth decade.

Rothstein and Welt (15) state that the duration of polyarteritis may vary from a few weeks to six months, rarely a year. In the case of one nine-month-old infant reviewed by them, the apparent duration of the disease was only four hours. Occasionally periods of remission and exacerbation occur. The mortality, as reported by these authors, was between 90 and 95 per cent. However, no significant series has been reported since the advent of steroid therapy.

From a study of forty-four cases in the literature and two of their own, Keith and Bagenstoss (8) stated that because of the bizarre manifestations of the disease, it is correctly diagnosed during life only in about 15 per cent of cases. The diagnosis is suggested by

one or more of the following symptoms: (1) a prolonged septic temperature which cannot be otherwise explained; (2) occurrence of symptoms in various parts of the body which can be related to arterial occlusion, as areas of gangrene and ecchymoses, and (3) appearance of nodules under the skin, particularly in relation to the smaller arteries.

The most common symptoms and signs were found to be: (1) fever (86 per cent of cases); (2) leucocytosis (63 per cent of cases with eosinophilia occurring in less than 20 per cent (3)); (3) abdominal and rheumatic pains (50 per cent), and (4) evidence of renal disease (40 per cent). These are followed in diminishing order of frequency by generalized weakness, convulsions, tachycardia, anemia, purpuric and other rashes, such as urticaria; hypertension, tonsillitis or other forms of sore throat, headache, intestinal hemorrhage, peripheral gangrene, signs of meningitis and palpable nodules.

Cohen *et al.* (5) stated that biopsy of a skin nodule or a tender area in a muscle will usually confirm the diagnosis. Bradley (4) reported a ten-year-old girl in whom the disease was suspected during life on the basis of the clinical data and the characteristic "telescopic urinary sediment" which appears to be typical of this type of vascular disease. This was described by Krupp (9) who stated that the urinary sediment in vascular angitis shows simultaneously the changes found in all three stages of the Addis classification of glomerulonephritis. These are red and white blood cells, red blood cell casts, oval fat bodies, granular casts, hyaline casts, and broad casts in a single urinary sediment accompanied by large amounts of protein.

Keith and Bagenstoss (8) agree with those who believe that the term "periarteritis nodosa" probably covers several diseases which are most likely only symptom complexes or syndromes. These are perhaps, as the pathology, which shows a wide variety of lesions, suggests, the result of various infectious or toxic agents. Among these are scarlet fever (11), rat bite fever (12), reactions to penicillin (1), and sulfonamides (13), therapeutic sera (13), etc. Rich and Gregory (14) have produced the disease experimentally as a manifestation of hypersensitivity. While the disease in adults occasionally occurs in association with asthma, so far as I know, this has not been reported in children.

Middleton (10) stated that the protean manifestations of periarteritis nodosa bespeak a background of sensitivity. Its eosinophilic reaction is limited to the blood vessels, a circumstance which places it outside the restricted purview of diffuse collagen disease. The vascular nodules involve the walls of the smaller arteries and are localized collections of white blood cells, fibrin and blood. Since they occur only in about 4.5 per cent of cases (8), it seems rather irrational to designate the disease "periarteritis nodosa." Polyarteritis is a much better term from the standpoint of the pathology.

Death is generally the result of complications of the disease, such as thrombosis and hemorrhage. Infarction and necrosis may be rapidly fatal depending upon the organs in which they occur. Renal insufficiency and pneumonia are also frequently fatal complications.

There is no specific treatment for polyarteritis and there was no symptomatic treatment of any value until the advent of ACTH and cortisone. Dent *et al.* (6) reported a nine-year-old boy who apparently recovered during a fifty-five-day period of therapy with cortisone, vitamins and aspirin. The hormone was administered after sulfonamides, various antibiotics and other measures had proved ineffectual. The patient was reported free of symptoms and progressing normally over a two-year period after withdrawal of the cortisone. Bagenstoss *et al.* (2) reported two adults who had been treated a short time with cortisone with temporary clinical improvement, but who later died. The lesions showed evidence of the same type of healing that occurs when the disease heals spontaneously.

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LUPUS ERYTHEMATOSUS

Lupus erythematosus is a disease of unknown etiology. Its onset has, at times, been associated with excessive exposure to sunlight, ultraviolet light from any source, including photographic light, trauma, exposure to x-ray, chrysotherapy or specific sensitivities (13). Michelson (12) has reviewed some interesting evidence that the disease may be of virus origin, but this has not been proven.

There are two distinct types of lupus erythematosus. One is essentially a skin lesion and is termed the chronic or discoid type. The other is a disseminated or systemic disease which may be very severe and is usually fatal, although 20 per cent of the patients are said to be alive five or more years after the onset (13). Between these two types are many gradations to which the term subacute lupus erythematosus has been applied. When the disseminated type is accompanied by endocarditis, it is sometimes termed the Libman-Sachs disease. About 85 per cent of the cases occur in females (13). Lupus erythematosus is rare in pediatric practice. Bassen (1), in a series of 111 patients studied by him from the hematological standpoint, found about 4 per cent in children.

The discoid, or "fixed" type, is described by MacKee and Cipol-

laro (11) as the most common. Its favorite location is the center of the face, where it causes the typical "butterfly" or "bat wing" appearance, and the ears and scalp. The lesions are sharply defined, violaceous in color and scaly, and may be accompanied by intense itching. Disseminated lupus erythematosus may be superimposed upon the chronic discoid type or may occur as a primary, acute systemic disorder accompanied by severe constitutional manifestations. According to High (9), in the primary acute form the face may be swollen and covered with multiform erythematous and purpuric papules, vesicles and bullae which may also involve the rest of the body. Constitutional symptoms are commonly fever, gastrointestinal symptoms, loss of weight and prostration. Arthralgia, which may be migratory, occurs in most cases.

Dermatopathologists are, Michelson (12) states, able to make a diagnosis of lupus erythematosus with reasonable assurance from a skin biopsy, but it is a diagnosis based on overall evaluation of the case and not on a specific finding. In the case of acute systemic lupus erythematosus the demonstration of the L. E. phenomenon, first described by Hargraves, Richmond and Morton (5) in 1948, offers a reasonably accurate diagnostic method for determining the presence of this disease. The L. E. phenomenon is seen in two stages in hematological smears (8): (1) rosettes of leucocytes around nucleoprotein, and (2) the L. E. cell, a leucocyte which has engulfed a round mass of nucleoprotein. A simple technique for demonstrating the L. E. cell on blood obtained by finger puncture has been described (15). There is some evidence, as reviewed by Bridge and Foley (2), that this phenomenon may rarely occur in other pathological conditions. Incidentally, these authors first demonstrated the presence of the L. E. phenomenon using fetal and cord blood in two cases where the mothers suffered from lupus erythematosus.

Downing and Messina (4) reported a death in a fifteen-year-old girl who first complained of loss of energy, general malaise and stiffness and soreness of the fingers for a few weeks. Tender, erythematous, inflammatory areas also developed upon the fingers. The typical "butterfly" lesion of the face soon appeared and she complained of abdominal pain, nausea, vomiting, muscular and joint pains. She died a few months later. Jacobs (10) reported a ten-year-old girl who died of hemolytic anemia complicating lupus erythematosus.

The treatment of lupus erythematosus is not satisfactory. Quinacrine hydrochloride (atabrine) (3, 14) and chloroquine sulfate (6) have been very helpful with the discoid type. In systemic lupus erythematosus bismuth and gold have been used, but the introduction of ACTH and cortisone has completely revolutionized the treatment of this disease. Haserick (7), in a comparison between steroid and non-steroid treated patients with similar degrees of illness, showed a dramatic, often life-saving effect on the severe fulminating course of lupus erythematosus which lead to a lengthening of life through the use of continuous, uninterrupted maintenance therapy and an improvement in morbidity. Certain patients were, however, not improved, especially those with progressive renal disease.

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PROGRESSIVE SYSTEMIC SCLEROSIS (GENERALIZED SCLERODERMA)

The term "progressive systemic sclerosis" was introduced by Goetz (5) in 1935 to replace the older, unfortunately chosen term of "scleroderma," as well as to describe more accurately the pathology of the disease. The term scleroderma is unfortunate because it is so easily confused with other similar descriptive terms for completely unrelated diseases, as, sclerema neonatorum, scleredema, and scleroma. In progressive systemic sclerosis the same changes take place wherever connective tissue is found (5). These consist of edema followed by proliferation of connective tissue in the form of collagenous bundles. The disease may occur rarely in childhood and its cause is unknown. Females are principally affected.

The prodromal symptoms of the disease are commonly weakness, weight loss and arthralgia. The cutaneous involvement characteristically passes through several stages from brawny edema to a smooth, tight, waxy skin which is not movable over the deeper tissues and, occurring about joints, may cause immobilization. Any cutaneous area may be involved; most frequently changes begin on the extremities, cheeks, bridge of nose, forehead and chest. Marked brownish pigmentation of the skin may develop, with anhidrosis, loss of hair and formation of indolent ulcers (10). The symptoms of visceral involvement are varied, depending upon the organs affected. The prognosis for life is generally fair and some patients have lived as long as thirty years (1). Remissions frequently occur. As a rule, laboratory data, other than skin biopsy, contributes nothing to the diagnosis. Circumscribed patches of the disease may occur in the skin in bands, sometimes following the course of the peripheral nerves, or in plaques termed "morphea." This is the more common type in children, but is also common in adults. Morphea consist at first of sharply outlined areas of hyperemia, varying in size from 1 to 8 cm., which later become ivory white. Usually they have a pale red border. The skin of the patch is hard and thick and cannot be wrinkled. Lesions of split-pea size are called morphea guttata (white spot disease) (10). Progressive systemic sclerosis must

be distinguished from progressive acrodermatitis chronica atrophicans. This disease usually starts with an erythema of the extensor surfaces of the limbs and the atrophic skin is slack (13).

There is no satisfactory treatment for this disease. Salicylates are useful for decreasing stiffness and joint pains. ACTH and cortisone have been of no significant help (1). Evans *et al.* (4) found no drug therapy as useful as the release of vascular tone by sympathectomy in selected patients.

SCLEREMA NEONATORUM has no known relationship to progressive systemic sclerosis and has not been described as a collagen disease. It is an uncommon disease of the newborn characterized by a diffuse, rapidly spreading, nonedematous, tallowlike hardening of the subcutaneous tissue of infants in the first few weeks of life (6). This disease responds dramatically to ACTH and to cortisone (3, 7, 8).

SCLEREDEMA is an unusual condition resembling progressive systemic sclerosis (2). The skin of the involved region becomes edematous and swollen, resembling the first stage of this disease but, instead of progressing to the indurative and atrophic stages, the process slowly regresses, leaving little or no residual change. Like progressive systemic sclerosis, it involves not only the dermis and subdermis, but also the fascia and muscles.

SCLEROMA is a term applied to a granulomatous process, primarily localized in the upper respiratory tract and secondarily appearing about the pyriform aperture of the vestibule of the posterior nares. Other parts of the respiratory tract may also be involved, including the larynx, lungs and also the heart (9). Because the disease most often involves the nose, it would cause less confusion if the term by which it was first described, "rhinoscleroma," were continued. It is rare in the United States. It is believed to be caused by a bacillus, *K. rhinoscleromatis*. The disease appears to respond to streptomycin (12).

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DERMATOMYOSITIS

Dermatomyositis is a systemic disease in which the skin, subcutaneous tissues, skeletal muscles and occasionally viscera are the sites of a non-suppurative inflammation, usually chronic in character (1). Rarely are the cutaneous lesions absent, in which case the disease should be called "polymyositis." Although not common in children, a series of twenty-six cases was studied by Wedgwood, Cook and Cohen (2) and it is from their publication that the material here presented is largely obtained. There were fifteen girls and eleven boys ranging in age from two to eleven years. Eight of the children who died did so between four and twenty-six months after the onset, suggesting that the disease process usually becomes inactive after this period. Eight of the children, while showing residual evidence of this disease (calcinosis, localized muscular atrophy, minor contractures or minimal skin changes), were able to lead normal, active lives.

No constant precipitating factors were observed. In two cases exacerbations occurred concurrently with manifestations of drug sensitivity to sulfadiazine and penicillin. The onset was commonly

insidious. Most of the children had the disease for weeks before medical advice was sought. However, occasionally the onset was acute. This was usually associated with extensive involvement, a rapidly progressive course and a fatal termination. The commonest early symptoms were weakness and easy fatigability. In only two cases was weakness not noted at some time during the illness. Weakness was associated with muscle stiffness, usually first noted in the lower extremities. There was soreness and pain in the extremities and occasionally in the joints. Usually, although not invariably, the process was irreversible when the weakness was extensive, and then it either terminated fatally or ended in marked crippling.

The most critical factor in respect to survival was the degree of involvement of the muscles of respiration and deglutition. Weakness of these muscles was noted in thirteen of the children and was the cause of, or contributed to, the fatal outcome in at least five. Fever, ranging from low grade to 39.5 C. (103.1 F.) was noticed early in the disease in eleven children and in only five had no fever been recorded.

Involvement of the skin of the face was observed in twenty-three of the twenty-six children and was usually present early in the disease. The characteristic lesion was a violaceous or erythematous discoloration of the upper eyelids (occasionally periorbital in distribution) associated with periorbital edema which at times extended to involve the bridge of the nose, the malar areas and the upper lip. A "butterfly" eruption, resembling that characteristic of lupus erythematosus, may occur. At times the erythematous lesions also involved the skin over the anterior chest and there was fine scaling of the involved areas. Deposits of calcium, apparently secondary to necrosis, were found late in the disease in the muscles, fascia and subcutaneous tissue of seven of the children. These deposits occurred in all but two children followed over a period of four years. When extensive, this condition is included in the syndrome of *calcinosis universalis*.

In those patients who survived, a major factor contributing to disability was contracture of the extremities. Adenopathy was not found more frequently than in the general population. As in the adult condition, to which the disease in children is very similar, it was only occasionally characterized by a series of remissions and

relapses. In most instances, exacerbations did not occur once the process became quiescent.

No diagnostic laboratory procedure except biopsy was found useful. Disseminated lupus erythematosus was the disease most commonly confused with dermatomyositis. Early in the disease a differential diagnosis may be difficult, and even a biopsy may not provide the answer. L.E. cells were, however, not found, and in no case did lupus erythematosus and dermatomyositis coexist in the same patient. Poliomyelitis, myasthenia gravis, muscular dystrophy, and other neuromuscular diseases have been confused with dermatomyositis, but usually the diagnosis becomes clear after a period of observation. There were five children in whom a diagnosis of localized dermatomyositis or morphea had been made. These children presented discreet areas of induration of the skin and subcutaneous tissues, muscular atrophy and local contractures without any of the generalized manifestations. It was felt that this condition was more closely allied to scleroderma. The disease has not been verified in infancy, although it has been suspected.

The follow-up studies ranged from one to nineteen years. Of the twenty-six children, ten were dead, four still had the active disease, four had crippling contractures, and eight were leading an active life. Thirteen of the children received endocrine therapy with ACTH, cortisone or testosterone. This appeared to produce at least symptomatic benefit in some cases, particularly early in the course of the active disease and, coordinated with symptomatic care, helped to tide the patients through the acute stage. Since death from this disease often results from palato-respiratory involvement, maintenance of an adequate airway and the use of a mechanical respirator may prove life saving. The most important treatment consists of persistent orthopedic measures and physiotherapy to minimize contractures.

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PSYCHOSOMATIC ASPECTS OF ALLERGIC DISEASE IN INFANCY AND CHILDHOOD

NO ONE now seriously questions the important role of the psyche in human disease of any kind. The problem, from the standpoint of therapeutics, appears to be that of determining its relative importance as an etiological or contributing factor, particularly in those disorders which have not responded to orthodox methods of therapy. It should be emphasized, however, that failure to respond to such treatment is by no means proof of a psychosomatic origin of the allergic problem. It simply means that, as far as the allergist is concerned, he has gone as far as he can and should therefore seek aid from the next source most likely to be of help which, in such instances, might be investigation from the standpoint of psychosomatics.

In infancy and childhood, asthma and atopic dermatitis (eczema) are the conditions most commonly studied by the pediatric allergist. In my own practice (see Table I) 92 per cent of 516 successive allergic children suffered from one or both of these diseases. The literature on psychosomatics does not point out any clearly defined psychological differences between individuals suffering from asthma and/or atopic dermatitis. This might be expected since, in the same individual, the shock organ, i.e., the skin or lungs, may alternate from time to time. For this phenomenon Ratner and associates (17) have originated the very apt term, "the dermal-respiratory syndrome." It was (and is) a common observation in folk medicine that as the skin of an eczematous individual clears, asthma is very likely to develop and this is termed the "striking in" or, in the older medical terminology, the "internal metastasis" of the eczema. This is not to say that distinct differences cannot occur in psychological characteristics between those individuals who suffer only from asthma or only from eczema or only from some other allergic disease. The young girl who suffers only from a disfiguring allergic

dermatitis may reasonably be expected to develop characteristics different from those of a girl of similar age who suffers only from bronchial asthma which, though severe, may interfere only at times with her various activities. The problems of both are different from those of a patient made a chronic invalid by ulcerative colitis. However, the psychological disturbances in these instances *result from* and cannot be regarded as *contributing causes* to these diseases, at least primarily. Eventually the psychological disturbances may contribute, perhaps as stress factors, to aggravate the condition, thus producing a type of vicious cycle.

The development of the concept of stress as the cause of allergic and other diseases through its effect upon the hypothalamus-pituitary-adrenal axis may perhaps eventually enable us to assign to psychological influences, at least in some instances such as the above, a probable place in the causation of allergic diseases along with other more tangible etiological factors. If this concept is accepted it is then easy to understand how in some instances psychic trauma alone can precipitate an allergic manifestation in an individual predisposed by hereditary or other unknown factors to allergic disease.

It is also reasonable to suppose, as has been indicated by Gerard (9), that there are individuals in whom neither the psychic stress by itself nor the allergen by itself can produce the asthmatic attack, but when both act together, an attack will result. This is analagous to the occasional situation where the child with ragweed pollinosis (hay fever) will not suffer from asthma unless he eats a certain specific food or is exposed to a particular animal or an overdose of house dust whereas these allergens will not cause asthma when the exposure occurs outside of the ragweed pollen season. It is a mistake to assume that psychic trauma is responsible for all or most allergic manifestations and their failure to respond to orthodox allergic management. It is obvious that at one end of the scale are patients in whom no psychosomatic factor can be reasonably demonstrated, as the infant in the newborn period, for example, who reacts with diarrhea, colic or atopic dermatitis to cow's milk and who loses this disability when changed to soy bean or meat base milk.

Bakwin and Bakwin (3) note that history taking in allergic children, in addition to the usual routine questions, should include infor-

mation on the relation of emotional episodes to the occurrence of an attack; the child's and parent's attitude towards an attack; the interparental relationships and the personalities of the parents, especially the mother; the parental attitudes towards the child with special reference to oversolicitude, overindulgence, overanxiety and rejection; the personality make-up of the child, especially as to anxiety, immaturity, dependence; the relation to the siblings; the amount and nature of restrictions on physical activity, and the relation to school.

Ruth Bakwin (2) further stated that most parents who bring their child to a physician are eager to pour out their troubles, and that this should be encouraged. From this the physician learns what is important to the parent and with what kind of a parent he is dealing. Discretion is necessary in obtaining data about parental attitudes towards the child. "How does the child behave?" is a most rewarding question. A parent who is sincerely satisfied with the child's behavior is unlikely to be a rejecting parent. Another useful question, Bakwin states, is, "Is he a happy or a moody child?" This may be followed by, "Did you have a happy childhood or did you have difficulties similar to those of your child?" Happy children do not have deep-seated emotional problems, and parents, satisfied with their own upbringing, are usually successful with their children. Inquiry as to how the child is disciplined, for what and what the reaction is, gives much information. Play interests and playmates are worth investigation because of the light thrown on the child's own personality. Something can be learned of his adjustments to the limitations imposed by his allergy. When the child seems well adjusted, the home happy, and emotional conflicts minimal, investigation need not be further continued. The degree to which psychologic factors influence the frequency and severity of asthmatic attacks, for example, in children varies widely. In many instances emotional factors are of no moment and the attacks are satisfactorily controlled by the usual technics. Under such circumstances it would be academic to be concerned about the psychic component.

However, as Bakwin further observed, where the anxiety, rejection and dependence are overwhelming, the family needs reëducation and reorganization. This is true with allergic as well as other children, and equally true whether or not the attacks are controlled

by medical treatment. To spend one year, not to say three or four, as detailed by some psychiatrists, in an attempt to cure asthma seems expensive and extravagant. However, if the prolonged treatment is necessary to relieve an abnormal emotional situation and the family comes out of the treatment as a healthy, integrated unit, the value cannot be doubted.

After the allergist has studied and treated his patient by all the usual methods without success, then one should in all fairness suggest that the patient also seek help from the psychiatrist, or employ such measures in this field as the allergist himself has been trained to use. Both the allergist and the psychiatrist should have sufficient humility to admit that there are *possible* etiological factors in the way of specific allergens which have been overlooked and which *might* be the cause of the patient's refractoriness. This has been illustrated many times in my own experience, as will be mentioned subsequently. Another aspect of the same situation is the disappearance of allergic symptoms believed to be of psychic origin when the disease is satisfactorily managed symptomatically by some new advance in therapeutics. Examples of this are the favorable responses of some cases of chronic urticaria of years duration which occurred when the antihistamines were introduced and, more recently, the satisfactory management of a disfiguring area of atopic dermatitis on the face of a young girl when hydrocortone ointment became available.

French (8), in 1941, stated that the psychosomatic situations which most commonly induce an asthmatic attack are: (1) threatened separation from the mother, a situation which is most commonly described as "maternal rejection" and which will be defined in detail subsequently; (2) rage, and (3) fear. Leigh (10), however, as a result of his review of the literature up to 1953, states that the impression is given that almost any emotional disturbance may bring on an asthmatic attack. At the present time, however, the concept of maternal rejection is perhaps generally accepted as the most important psychologic factor contributing to asthma in the child. This subject has been dealt with particularly by Miller and Baruch (11, 12, 13, 14) who, in studying the mother-child relationship in allergic children, and particularly asthmatic children, reported the cases of ninety allergic children (fifty-five asthmatics,

thirty with hay fever and five with eczema) compared with a group of fifty-three psychiatrically disturbed children. In the allergic group maternal rejection was found in 98 per cent of the children, whereas in the control group this was found in only 24 per cent. Maternal rejection was considered to precede the onset of the allergic child's illness in 96.5 per cent of cases. Similarly, marked differences in the expression of hostility were found to exist between these two groups of children: 83 per cent of the non-allergic children expressed hostility to the parent or parents as compared with 20 per cent of the allergic children. It is also stated that the allergic child, although rejected by the mother, is unable to express his hostility to her, and often turns it in towards himself with a resulting asthmatic attack. However, Leigh (10) goes on to point out that much of the material from which these conclusions were drawn is largely subjectively determined, depending upon the interpretation of play, the assumption that certain behavior is linked with certain emotions, and that asthmatic attacks are causally related to the mother-child relationship.

In her moving little book, *One Little Boy*, Dorothy Baruch (4) beautifully details a case report of the management of an asthmatic child by the psychosomaticist with his eventual triumph over asthma. However, as a pediatric allergist, I am inclined to view this with some skepticism, since it is mentioned occasionally in the book that Kenneth, the little hero, had a dog. I have had too many experiences with children with asthma who gave negative skin reactions to the animal's dander, who did not react to the animal clinically in an obvious manner, and who, nevertheless, recovered only when through accidental death or otherwise the animal was eliminated. One wonders about the possible relationship of this to Kenneth's recovery from asthma.

Williams (18) has discussed the management of atopic dermatitis in children by the management of the maternal rejection factor. It is carefully explained that this represents only one of the many facets of the difficult problem of atopic dermatitis. There are two principal definitions of the term, "maternal rejection." Newell (16) defined it as "that situation where the birth of the child was unwelcome to the mother." In a broader sense Figge (7) stated that "a rejecting mother is one whose behavior toward the child is such

that she consciously or unconsciously has a desire to be free from the child and considers it a burden." In his study the rejection did not take the form of overt neglect but was, rather, an accumulative effect of a continuing irritability towards the child expressing itself as frustrating, nagging and scolding, emotional explosions and "scenes," unreasonable discipline, insistence on petty regimenting detail, an attempt to overpower the child's will, a running battle each mealtime over eating habits, and, above all, a striking lack of the demonstrative love expressed by the enfolding arms, the loving caress and the "soft word" that "turneth away wrath" (hostility).

Mohr and associates (15) stated that: "Common features in the family constellation of the asthmatic child have impressed us strongly. The mothers . . . (exhibit) certain characteristic traits and attitudes with remarkable uniformity. They are highly narcissistic women, ambitious for themselves and children—they present ambivalent and rejecting attitudes toward their children—the mothers consistently dominate the domestic life." The fathers are described as being passive personalities "not actively interested in their children . . . who play a relatively unimportant role in the training and care."

Williams stated that in the study which he presented, the picture of the family group could not be as sharply detected but the general resemblance to the above description was more than coincidental. The clinical material for his study consisted of fifty-three children (twenty-two boys and thirty-one girls) between the ages of thirteen months and twelve years with chronic "flexural eczema." These had other characteristics which definitely placed them in the group of children with chronic atopic dermatitis. The clinical material was divided into two groups. The first group comprised thirty-three children, and here the therapeutic emphasis was on management of the maternal rejection factor. The second, or control group, consisted of twenty children without any direct or indirect approach with regard to personality type, emotional reactions or the interpersonal relationship with the child and the mother. Generally speaking, these were treated as children are commonly treated in the office of the allergist. None were treated, however, with roentgen rays.

The results of these treatments are indicated in Table XXIII.

TABLE XXIII

Therapeutic Response of Fifty-Three Children with Atopic Dermatitis,
Followed for Twenty-Four Months

<i>Type of Therapy</i>	<i>No. Free from Dermatitis</i>	<i>No. with Improvement in Dermatitis</i>	<i>No. with Dermatitis Unchanged</i>	<i>Total</i>
Management of maternal rejection	15 (45%)	15	3	33
Control	2 (10%)	14	4	20

Of the three children in the group in which maternal rejection was emphasized who were unimproved after twenty-four months, two lived in disturbed homes with irreconcilable tension between the parents and in the third instance the mother was very hostile to the idea that she might be unwillingly playing a role in the child's distress and insisted that the child was allergic to foods, though she couldn't specify any food items nor could she help the child's dermatitis by manipulating the diet. Of the fifteen children who were improved, six lived in turbulent home environments with continuing parental emotional instability and friction.

In the control group only one mother felt that any food had any bearing on the dermatitis. In no other instance did it appear to play any clearly discernible part in causing or aggravating the dermatitis, nor was there any clear cut evidence that airborne allergens played an etiological role, with the exception that any aggravation in many children might be interpreted as a result of an increased exposure to house dust. As Williams stated, the number of children in the study was not large enough to draw more than a few simple statistical deductions based on certain suggestive differences. The number of children, only two out of twenty, in the control group who became symptom free could, he stated, simply reflect his personal inability to manage atopic dermatitis with the so-called "orthodox treatment." In my own opinion, the control group here has little validity since it should have been managed by a pediatric allergist as well as a dermatologist.

In the treatment of the test group some perhaps oversimplified advice was given to the mother and just how practical this is can be determined only by future experience. There is, for example, no way that a mother can be assured of being well rested, in good

health and enjoying a good partnership with the father, and, certainly in my opinion, true affection cannot be prescribed. However, in a situation like this there is little to lose in making the effort:

(1) By being in good health and well rested. Hours of sleep should be continuous and adequate, the father doing any necessary night vigil. The "jet propellers"—tea, coffee and colas—should be restricted and mild sedation given.

(2) By enjoying a happy partnership with the father in an "even" home. Emotional explosions and scenes between marital partners, particularly before the child, are disastrous. Separation and divorce produce and aggravate maternal rejection.

(3) By expressing affection for the child frequently each day by the enfolding arms, the caress and tender words.

(4) By spending at least five tender minutes at the child's bedside each night. Doing so provides the best sedative an atopic child can be given before being cut off from the mother by darkness, uncontrollable dreams (frequently fearful) and the nocturnal distress of pruritus.

(5) By avoiding unreasonable, harsh discipline and following all verbal or corporal disciplinary action promptly within a few minutes with maternal forgiveness expressed by a reasonable explanation for the disciplinary action and by the enfolding arms, caress and the tender word.

(6) By avoiding the use of frustrating, restrictive commands, threats, and expletives, such as "No, don't do that!" "Stop it!" "Leave it alone!" "Get out of my way!" and "You make me sick!", which are frequently showered daily on the atopic child by the tired, irritable mother.

(7) By deftly avoiding any "clash of wills" or "joining battle" on any "issue" raised by the resistive, hostile atopic child, whether it be "eating peas," "wearing that blue dress," or "not touching that piece of Dresden," for example.

In the discussion which followed William's presentation Osborne stated that he had yet to see an excellent or a good result obtained by the treatment of atopic dermatitis by a psychiatrist. This has also been my experience and Dees (6) has made essentially the same statement. Binkley also expressed an opinion which is held by most pediatric allergists to the effect that the basic problem in atopy is the

allergen contacting a sensitized individual. He used the example that just as the catalyst nickel accelerates the hydrogenation of vegetable oils to produce solidified fats, so the maternal rejection factor is a catalyst in producing atopic dermatitis. There are, however, many other catalysts of importance as temperature changes, detergents, fatigue, infection, and trauma, to mention a few. Brunsting emphasized the point that a child who is disfigured by atopic dermatitis is an object of concern not only to himself but to those who are closely related with him, as his siblings and playmates, and his psychological reactions are intensified by the cruel rebuffs that he meets with and the rivalries that are set up. Michelson also expressed another point of view which is held by the majority of pediatric allergists. This is to the effect that a family would probably get along very nicely if the child did not have eczema, and, since the eczema goes on, the tension is increased and cannot be attributed to any other cause than to the disease itself. Sympathy for the child is a fine thing but these children must be raised to live in this world. They are not going to live in an isolated atmosphere manned by trained parents. If the mother makes a child dependent upon her love, he is going to be in a very bad way when he does leave home.

The unique investigations of Bowen (5), who found that only one identical twin in each of fifty-two sets was affected by allergy, poses an interesting problem for the proponents of maternal rejection. Bowen asks the pertinent question as to how a parent would reject one twin and accept another. He also quotes Dr. Harvey Black who, after treating a nurse for pollinosis for a period of three summers, was asked the following: "I know my mother didn't like me too well as a child but why did she reject me only during the month of September?"

In conclusion, Abramson (1), whose experience in psychiatry as well as in allergy is considerable, has presented the point of view that the psychodynamic theory of maternal rejection is often not only incomplete but may frequently be misleading in treating the allergic responses in children and adults. He holds that the allergic child is not primarily rejected by the parents but rather that the opposite may occur; that the disturbance in the parent-child relationship is not parental rejection but rather mutual engulfment (introjection), and that rejection may occur when the mutual engulfment fails to satisfy the parental needs. As a pediatric allergist with-

out special training in psychiatry, Abramson's idea is certainly much more in accord with the general impression I have gained through the years than is the theory of maternal rejection. I have, perhaps, lost sympathy to a certain extent with the psychosomatic approach, although I have never doubted its value in thoroughly competent hands, because I have seen it so often abused by neglect of the somatic aspects of the problem. However, I am sure that the psychosomaticist could just as reasonably in many instances make the same criticism in reverse of the allergist.

It is hoped that eventually the allergist and the psychiatrist may succeed in reconciling these apparently directly opposed points of view. Meantime with one school of thought favoring maternal rejection and the other an apparently contrary conception, further confusion is added to a subject which is already highly confused in the minds of most physicians and thus further discredit reflected on the specialty of allergy in general.

The application of a psychological approach to problems of allergy in pediatrics is exceedingly difficult and is to be greatly encouraged. The general principle that a chain is no stronger than its weakest link holds true here. Under stress and strain of psychic origin the weakest link will give way and in the case of an allergic child an allergic response may logically be expected. The child with an allergic manifestation will soon discover that he can use this as a defense in a difficult situation in the same way that any other child with any other illness can use that particular illness. In proportion as a child's allergies have failed to respond to the efforts of his physician, so will a child feel less and less secure—a situation which is worsened by expressions of increasing anxiety on the part of the parents as this state of affairs becomes increasingly manifest. That abnormal psychological situations should develop under such circumstances is only natural. Probably, in most instances, with children the best that can be hoped from the psychological approach is amelioration, rarely a cure, because no psychological approach can ever change the underlying constitution responsible for the expression of stress as an allergic disease. A basically psychopathic individual may be expected, if his allergic difficulties are relieved, to express his clinical manifestations in some other form. Once we are able to relieve the allergic manifestations at will, the psychologic

problems will in many instances solve themselves. This does *not* mean, however, that the pediatric allergist should wait for this highly to be desired state of affairs. In fairness to his patient he should seek the assistance of the psychiatrist in his difficult cases in an attempt to remove all possible stress which might be detrimental to the patient's well-being.

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DIETARY TREATMENT OF ALLERGIC DISEASE

Preliminary Considerations

BEFORE discussing the dietary treatment of allergic disease we shall first consider some general principles in the dietary treatment of allergic infants in general. Since in early infancy foods are the most important allergens, some special consideration of those commonly first taken by the newborn infant, i.e., breast milk and cow's milk, is in order. This involves four factors of considerable interest to the pediatric allergist:

- (1) The possibility of hypersensitivity to human breast milk.
- (2) The passage of foreign proteins through human breast milk.
- (3) The passage of drugs through human breast milk.
- (4) The passage of foreign proteins through cow's milk.

HYPERSENSITIVITY TO HUMAN BREAST MILK

This condition, which seems like a most unnatural state of affairs, has been reported both in mothers and in infants. Duke (6) has described several cases in which the presence of milk in the breasts caused allergic manifestations in the mother and in one instance these were not relieved until the patient received hyposensitizing injections of breast milk extract.

There are several scattered reports of infants very sensitive to breast milk on ingestion. Kerley (15) mentioned twins born of a mother who was sensitive to cow's milk. One of the twins reacted on the ingestion of cow's milk; the other of breast milk and had to be weaned. No other details were given. Campbell (3) reported the case of a newborn infant whose older brother was said to have died of anaphylactic shock after his first breast feeding. This infant presented similar symptoms when one drop of his mother's milk was placed upon his tongue. He was promptly weaned. Another new-

born infant was placed on the breast the second day of life and immediately went into a state of anaphylactic shock requiring the injection of epinephrine and artificial respiration for resuscitation. The same thing occurred the following day when he was given one drop of his mother's milk. He was immediately weaned and later gave a positive reaction to human breast milk on skin testing.

Wergeland (30) divided intolerance to human milk into two categories, intoxication and allergy. Human milk may acquire toxic properties if during pregnancy the mother's diet is deficient in Vitamin B₁₂ and such milk may produce an intoxication in an infant which may run a fatal course. This disease is important in some parts of China where it was at first termed "infantile beri-beri" but is now correctly called "breast milk intoxication." Allergy may be either to substances passing through the breast with the milk or specifically to human breast milk protein. Wergeland reported three cases of apparent allergy to human milk in the newborn occurring over a period of three years in the same family. The chief symptoms were vomiting and intractable diarrhea. All three infants had the same symptoms on cow's milk. In the case of the third child, soybean milk substitution was tried. The infant did remarkably well at first but apparently became sensitized to soy bean and eventually died in anaphylactic shock.

In my experience I have not yet encountered what I have felt was definite clinical allergy to human breast milk protein. In the routine skin testing of allergic infants with this protein I have had but one positive reaction. This was in the case of an infant with atopic dermatitis who also reacted to cow's and goat's milk, and to egg and a number of other less important foods. By way of experiment the infant was left on the breast and all other reacting foods removed from the diet of the mother. The child cleared nicely so that in this instance the positive skin test was of no clinical significance.

There is, of course, no reason why an infant should not be allergic to the specific human protein of breast milk, but the actual proof of this is a difficult matter. A positive skin test to human breast milk is only presumptive evidence and is not proof of clinical sensitivity as indicated in the above paragraph. It is well known, as will be discussed shortly, that food ingested by the mother may pass through

the breast milk and cause allergic manifestations in the infant who happens to be sensitive to those foods. This being the case, proof of allergy to human breast milk would require that the mother be kept on a special diet while nursing. If, for example, she were on a diet consisting exclusively of a milk substitute containing no allergens whatsoever except those derived from the soy bean, and her infant gave allergic reactions to her breast milk but could tolerate the same soy bean milk substitute fed the mother (provided other infants could tolerate this breast milk), one would have very strong evidence indicating sensitivity to human breast milk. Such controlled experiments have, however, not yet been published.

TRANSMISSIONS OF FOOD PROTEINS THROUGH BREAST MILK

The transmission of food proteins ingested by the mother through the breast milk with the production of allergic manifestations in the nursing infant sensitive to those foods is now a well-recognized phenomenon. Talbot (27), in 1918, reported the case of a nursing infant in whom eczema would occur when the mother ate chocolate and would disappear when the chocolate was removed from her diet. O'Keefe (19), in 1920, found that some nursing infants with eczema gave positive skin reactions to foods they had never eaten and in some instances recovery from eczema was prompt when these foods were removed from the mother's diet. Shannon (23), in 1921, described a seven-month-old nursing infant with urticaria. The child gave several positive skin tests to foods and when these were removed from the mother's diet the skin rapidly cleared. Among the foods to which the child reacted was eggwhite. The mother was fed eggwhite and her breast milk obtained after the feeding caused anaphylactic shock in a guinea pig sensitized to eggwhite. The following year Shannon (24) reported eight cases of eczema in nursing infants due to foods ingested by the mother. Later Donnally (5) demonstrated by passive transfer tests the presence of egg antigen in breast milk thirty minutes after the ingestion of eggwhite by the mother. Brunner and Baron (2) by means of the passive transfer technique noted the passage of cottonseed protein through the breast milk. Ström (26) reported urticaria in nurslings from orange juice fed the mothers and one case of urticaria in a nursling due to chocolate fed the mother. It is quite probable that almost

any food the mother ingests will cause allergic reactions in the nursing infants if the latter is sensitive to that particular food.

The reason why infants and very young children may react to foods which they have never ingested may perhaps be explained on the basis of three possibilities:

(1) **INHERITED SENSITIVITY:** There is no evidence that the human infant can be passively sensitized to foods in utero. It seems quite evident, however, that active sensitization does occur. This has been fully discussed in Chapter 6 and need not be further considered here.

(2) **SENSITIVITY TO OSMYLS:** Food odors and vapors may cause allergic reactions. Odors are propagated by very minute particles of matter called osmyls and these may act as allergens to produce allergic reactions in highly sensitive individuals (9, 10, 11). Cazort (4) and Epstein (7) have reported children so sensitive to egg that it was necessary not only to be sure that no eggs were brought into the house, but in some instances the parents could not even eat eggs outside of the home and on returning then play with their children without causing allergic reactions. Since this is true one must consider the possibility of sensitizing an infant by exposure to osmyls, so that a reaction would be obtained by skin test or clinically to a food the child had never ingested. An analogous situation is indicated by the work of Ratner *et al.* (20) who have shown that guinea-pigs may be sensitized by inhalation to horse dander. They gave evidence that this is doubtless the mechanism in certain instances in man.

(3) **SENSITIVITY AS A RESULT OF BIOGENETIC RELATIONSHIPS:** As emphasized by Vaughan (29), there is a biogenetic relationship between various families of foods in that they contain a common antigen. The individual who is sensitive to one food of the group may react because of this to other foods which he ingests for the first time. Such relationship is most marked in the case of closely related foods, such as the citrous fruits, for example. It is present but less marked in the case of the cereal grains, wheat, rye, corn, oat, and barley, which are all modified grass seeds. It is also not uncommon, in taking a history to find dislikes or disagreements of the individual to various members of the mustard family, which includes broccoli, Brussels sprouts, cabbage, mustard, radish, and turnip.

TRANSMISSION OF INJECTED POLLEN EXTRACT THROUGH THE BREAST MILK

There is no reported case of an inhaled allergen having been transmitted through the breast milk. Pollen extract injected into the mother may, however, be so transmitted. Sterling and Fishman (25) reported the case of a nursling whose mother was receiving injections of pollen extract. This apparently caused sneezing and dyspnea in the infant. Jones, Lowance, and Matthews (14) described a similar case in which sneezing without dyspnea occurred. Campbell (3) noted a nursling who would develop such severe eczema following the injection of pollen extract into the mother that her treatments had to be discontinued.

TRANSMISSION OF DRUGS THROUGH THE BREAST MILK

It is now well known that many drugs administered to the nursing mother will pass through with the breast milk and thus be ingested by the infant. This subject has been reviewed by Houts (13) and by Sapeika (22). There is no evidence that alcoholic beverages taken by a nursing mother may affect the infant. Habitual and excessive smoking on the part of the mother does not appear to have a harmful effect as far as the transmission of nicotine through the breast milk is concerned. Aloin, calomel, phenolphthalein, rhubarb and senna when taken by a nursing mother in therapeutic doses do not have a laxative effect upon the infant. Cascara will. As far as sedatives are concerned, codein, demerol, morphine and opium appear to be harmless but bromides taken by the nursing mother may produce their therapeutic effects in the infant. Sulfonamides pass through the breast milk in traces insufficient to produce therapeutic effects in the infant but probably in sufficient quantities to produce effects if the infant happens to be sensitive to the drug. The same is essentially true regarding penicillin. Sodium salicylate and quinine may be taken without harm to the infant. There is some experimental evidence that the metals arsenic, lead and mercury may be transmitted through the breast milk. The passage of iodine through the mother's breast milk has been confirmed by the feeding of radioactive iodine to the mother and demonstrating its presence in the breast milk (18). Thiouracil (3) is the only known drug found in larger concentrations in breast milk than in any other body fluid.

Since drugs can be transmitted through the breast milk it is not surprising to find that allergic drug reactions may occur in nursing infants, although this happens but rarely. One of the first recorded cases is that of Van der Bogert (28) who described a papulopustular bromide eruption in a six-month-old baby on the breast due to bromides ingested by the mother. Even more remarkable is the production of a bromide rash in the infant when the mother took the drug without manifesting cutaneous reaction to the drug herself. Such a case was reported by Yeung (32). In this instance the mother was given bromides because of toxemia of pregnancy. The rash appeared in the nursing infant ten days after delivery after the mother herself had stopped taking the drug. This indicates that the drug was not passed to the fetus in utero but mainly through the breast milk. Withholding the mother's milk resulted in rapid recovery. French (8) also stated, without giving specific references, that "bromide and iodide eruptions have been recorded in infants at the breast when the mother has been taking the drug without herself presenting any cutaneous symptoms." Maruri and Maruri (17) have also reported ioderma in an infant transmitted by the mother's milk.

The above suggests that in the presence of rashes of unknown origin in nursing infants at any age the possibility of a rash due to a drug ingested by mother has to be considered in the differential diagnosis.

TRANSMISSION OF FOREIGN PROTEINS THROUGH COW'S MILK

It is well known that toxic symptoms may be produced in man by the ingestion of milk or milk products from cows who have eaten the rayless goldenrod or the white snake root (1). However, the evidence that allergic symptoms may be produced by allergens ingested by the cow and passed through into the milk is very scanty. Rohrbach (21) in 1925 reported three cases of gastrointestinal disturbances in infants and two of eczema which were relieved by using the milk of cows placed on special diets. One other infant with urticaria and another with a gastrointestinal disturbance were relieved by using butter from a different source than that previously used. Hermann (9) stated that previously sensitized guinea-pigs react

by anaphylactic shock to the intrathecal injection of milk containing ragweed pollen protein. Ragweed allergen containing milk gives a positive cutaneous reaction in high dilution in sensitive persons. Ragweed pollen protein is found apparently unchanged in the milk of cows that have eaten ragweed tops some hours earlier. Ingestion of such milk produces clinical hay fever within one-half hour. Lyon (16), on the contrary, described a nursing infant who had angioedema due to white navy bean and corn in the mother's diet. At the age of two years the child would still develop angioedema on the ingestion of white navy beans. As an experimental measure a cow was fed white navy beans and corn for two weeks. During the second week this patient, a girl, was fed from 24 to 32 oz. a day (710 to 796 cc.) of fresh, unboiled milk from this cow and with no reaction. A few days after completion of this experiment she was again fed white navy beans and urticaria and angioedema developed as usual. In this instance there was no evidence that symptoms could be produced in a susceptible individual by a food ingested by the cow on drinking her milk afterwards. Further observations must be made on this interesting problem before a definite answer can be given.

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CHAPTER 61

COW'S MILK—GENERAL CONSIDERATIONS

THE CHEMISTRY of cow's milk with special reference to factors of most interest to the allergist has been reviewed by Lewis and Hayden (9). They stated that four proteins have been isolated from milk which have been found to be chemically and immunologically distinct. Casein, a complex calcium salt containing phosphorus, occurs in colloidal form and is readily separated from the whey proteins by the addition of dilute acids. The whey proteins, lactalbumin and lactoglobulin, can readily be "salted out" of the whey solution, and the fourth, the alcohol-soluble protein, is obtained from freshly precipitated casein by extraction with from 50 to 70 per cent ethyl alcohol. The alcohol-soluble fraction, although derived from casein, is not a cleavage product and is a fairly active antigen. I know, however, of no clinical studies of this milk fraction.

Although casein has no counterpart in serum, the whey proteins are biologically similar to the serum proteins of the animal from which they are derived. This is due to the presence of lactoglobulin, which is serologically related to the serum globulin. Only a small quantity of lactoglobulin is present in milk, while larger quantities are present in colostrum, and it is because of its presence that milk at times sensitizes to beef serum. The reaction does not always occur since only small amounts are present in milk and, as Lewis (8) has shown, when a small amount of an antigen has been injected into an animal together with excessive amounts of another antigen, the former may be prevented from manifesting its antigenic activity. Lactalbumin and serum albumin are chemically and immunologically distinct.

Hill (6) was unable to confirm the statement commonly made in the literature that cow and goat milk lactalbumin are completely immunologically distinct. He quoted von Versell (17) to the effect that while human and cow lactalbumin were found to be completely species specific, this was not so clearly the case in animals as closely related as the cow and the goat. Hill's investigations

also indicated that cow and goat lactalbumin are not entirely species specific. This is doubtless why although goat's milk has a definite and valuable place in the treatment of infants hypersensitive to cow's milk, it will not help in every case even when, presumably, the sensitivity is due to lactalbumin. However, lactalbumin is markedly heat labile since there is a decrease in antigenic reactivity even at 60 °C., which becomes progressively more marked as the temperature is increased (9). This explains why evaporated cow's milk, in which the lactalbumin is practically completely denatured by heat, is as satisfactory in most instances as goat's milk in the feeding of milk-sensitive infants.

Lewis and Hayden (9) further state that casein has been shown by immunological experiments to be as distinct from the whey proteins and serum proteins of its own species as it is chemically. A closer biological and chemical relationship exists between caseins derived from widely different species than between casein, whey and serum proteins of the same species. Although even the delicate method of spectrophotometric comparison of different caseins has shown that they are practically identical, Dudley and Woodman (4) demonstrated by a study of the products of racemization, that there are some structural differences, probably depending upon the position of certain amino acids in the molecule. Anderson *et al.* (1) carried out experiments indicating that cow's, human, and goat's caseins sensitize against each other. Their studies also showed a close biologic relationship between these caseins of different sources and suggested that this similarity may explain certain difficulties that are encountered in the treatment of milk allergy by the substitution of the milk of one animal for that of another. Casein, moreover, is relatively heat stable, no change being noted in its antigenic activity until the temperature reaches 100 °C. (9). The changes then taking place probably explain why, on rare occasions, super-heated cow's milk is occasionally tolerated by cow's milk sensitive infants. It is interesting in this connection that heating alters some antigens in that they give rise to antiserums which are more or less specific for the heated antigens, the so-called "coeto-antigens" (5).

The true incidence of allergy to cow's milk in infants is not known. Clein (2) stated that one infant out of every fifteen is allergic to cow's milk in some degree. In my practice, the incidence is at

least that high. However, in both instances, this is the practice of the pediatric allergist and a high incidence of allergy to cow's milk as well as other allergens could reasonably be expected to occur. On the other hand, in the practice of the general pediatrician, blissfully oblivious in most instances to the minor evidences of milk allergy, the incidence of this condition would be estimated as considerably less than it really is. The incidence as determined in Clein's practice, and estimated in my own, therefore probably represents a maximum. Loveless (10) has conducted studies which probably represent the minimum. She sent out questionnaires to 142 physicians belonging to the American Academy of Pediatrics or the American Academy of Allergy. They reported that 4,260 of their patients showed cutaneous allergy to milk. Since they were attending nearly 180,000 individuals, this meant an incidence of 2.3 per cent. However, it need hardly be pointed out that a positive skin test does not prove allergy to milk. In my experience, the great majority of milk-sensitive infants do not respond positively to scratch tests with milk; I do not use the intradermal test because so many false positives occur. To the figures above reported Loveless added those of another forty-nine pediatricians who do not perform cutaneous tests to diagnose food allergy and found that the incidence of milk hypersensitiveness amounted to only 1.5 per cent among nearly 250,000 patients. Figures were not included for Randolph, Rinkel, and Rowe or their followers. The result would have been considerably altered, for these men arrive at incidences five to ten times higher by the use of the food dairy, and ingestion and elimination procedures in combination with atypical symptoms. Thus the range of milk allergy is probably somewhere between 1.5 per cent as a minimum and 7 per cent as a maximum. The true figure will never be determined until the general pediatrician is thoroughly familiar with the varied symptomatology of allergy to cow's milk.

SEVERE IDIOSYNCRASY TO COW'S MILK

Severe idiosyncrasy to cow's milk of the anaphylactic type occurs but is, fortunately, uncommon. A classical description of this was given by Dr. Edwards A. Park (12) in 1920. The first symptoms occurred when the child, previously breast fed, was given a substi-

tute feeding of cow's milk at the age of six weeks. He vomited, turned pale and became drowsy. At the age of twelve weeks scratch tests to cow's milk were negative but the baby appeared to develop a mild, generalized reaction characterized by drowsiness and loose stools as a result of the testing. Only three days later, for reasons which were not explained, intradermal tests were done with a number of proteins, none of which gave immediate reactions. However, there was a marked delayed reaction at the site of the test to cow's milk which was not observed until four hours later, at which time the child had a severe generalized reaction characterized by pallor, stupor, vomiting and prostration. Three weeks later he was by error given two or three drops of a solution of condensed milk, one part, and water, twelve parts, and almost died of anaphylactic shock. At about the age of six months, the supply of breast milk failing, the boy was uneventfully completely weaned to goat's milk over a two-month period. Clinical sensitivity to cow's milk was still present at the age of twenty months when this case report was made. While Park stated that no record of the baby's having received cow's milk at the maternity hospital could be found, such a possibility could not be excluded. It was his belief, however, that the hypersensitivity in this case was prenatal and inherent in the germ plasm of the infant.

It is interesting, for reasons discussed above, that because the baby could tolerate goat's milk but not cow's milk the hypersensitivity was principally to the lactalbumin fraction of the milk rather than the casein. This appears to be the usual case when idiosyncrasy of the anaphylactic type is encountered to milk. However, all the facts in such cases are not known. Hill (6) stated that the immunological situation in many of these infants seems to be somewhat different than in those with eczema. They are not likely to have other sensitivities and they often give more negative than positive skin tests to milk, in spite of exquisite clinical sensitivity.

Kerley (7) saw one death from milk allergy in a baby ten months of age. At this time, in an attempt at weaning, 60 cc. (2 oz.) of cow's milk were administered by forced feeding. The child immediately went into collapse and died. Kerley also mentioned another infant three months old who almost died of anaphylactic shock when seven drops of milk were placed on her tongue.

I have had but one personal experience of this type. This was a three-week-old infant who, shortly after a few feedings of a cow's milk formula used to complement a failing breast supply, developed very alarming severe angioedema. The cause of the condition was immediately suspected, the child hospitalized, given supportive therapy, placed on soy bean milk and made a good recovery. On direct skin testing at this time the child gave very large positive scratch reactions both to lactalbumin and to casein. This is quite remarkable because strongly positive cutaneous reactions to casein are quite infrequent. The direct testing was confirmed by passive transfer.

The general subject of sensitivity to cow's milk has been reviewed by Von Sydow (15) and by Vendel (16). There are also many articles in the American literature on the great variety of symptoms which may occur in early infancy from the ingestion of cow's milk (2, 3, 11, 13).

COW'S MILK SENSITIVITY IN A LOWER ANIMAL

It is of considerable interest and not inappropriate at this time, before leaving the subject of cow's milk sensitivity, to briefly report Schroeder's case (14) of a young female walrus who was captured at an early age on the ice floes of Bering Sea. She was taken to the pools of the Zoological Society of San Diego where she was fed with meticulous care on evaporated cow's milk, according to the best practices in human infant feeding. Presently a considerable variety of pathologic features manifested themselves. They included skin disorders (reminding one of the eczematous manifestations of allergy in childhood) and disturbance of the mucous membranes, as rhinitis. All attempts at relief by changing the physical environment and care of the animal failed until cow's milk was eliminated from the diet. Immediate and permanent relief followed. If the reader is interested further in the subject of allergy in lower animals, the very fine review of Wittich (18) should be consulted.

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GALACTOSEMIA

Galactosemia is a disease, frequently familial, in which there is a congenital inability to metabolize galactose normally. This carbohydrate, derived from the lactose of milk, accumulates in the blood giving rise to enlargement of the liver, often jaundice and commonly death in early infancy. The disease should also be considered in older children in whom defective mentality is associated with cataract or liver disease. Galactosemia should be suspected if a reducing substance which analysis proves to be galactose is found in the urine. The diagnosis is confirmed if the galactose tolerance test is markedly elevated. The glucose tolerance curve is within normal limits. The urinary and blood findings with respect to galactose and the symp-

toms of the disease, except those due to organic changes, are largely reversible when lactose and galactose are withheld from the diet.

Galactosemia has been thought to be rather uncommon and Cox and Pugh (2) stated that up to the end of 1952 only twenty-five cases had been reported. However, since then there have been many reports of this disease, particularly in the American literature, and Bain and associates (1) have recently added eight more. For a review of the literature of this subject reference is made to the communication of Hsia and associates (4).

Forbes (3) has made the very interesting suggestion that possibly some forms of intolerance to cow's or human or any other mammalian milk might be due to galactosemia rather than to allergy or other causes and that such intolerance might in some instances represent "formes frustes" of the malady. Bain and associates have suggested that the diagnosis is frequently missed because, at the time of admission to the hospital, the infant is usually suffering from diarrhea, vomiting or severe malnutrition (symptoms which, as Forbes indicated, may be due to allergic intolerance to cow's milk) and is given only glucose drinks. Consequently the initial urinary analysis does not give the essential clue to the reducing substance which appears only when the baby is receiving milk feedings. Since the initial urine analysis is negative, it may not be repeated after the milk feedings have been started, thus further contributing to the error in diagnosis. Forbes further pointed out that because such infants do well on milk-free diets, this is considered as additional evidence that the child's trouble is due to allergy to cow's milk.

That "formes frustes" may occur is suggested by the communication of Lockhart and Roboz (5) who diagnosed a case in a four-day-old infant suspected because galactosemia had been previously diagnosed in a sibling at the age of three and one-half months. In this particular instance, the infant's paternal grandfather was said to have a "milk intolerance" the symptoms of which were nausea, malaise, and weakness occurring soon after milk ingestion and persisting for twenty-four hours or more. He also had occasional urinary sugar. This fits in with the note by Townsend and associates (6) to the effect that galactosemia is a deficiency which may become less severe as the individual matures but from which he

never fully escapes. It is also possible that some disorders diagnosed as neuroallergy may represent manifestations of galactosemia.

Forbes' suggestions are highly provocative and deserve the careful consideration of all physicians dealing with suspected allergy to milk, especially if accompanied by a reducing substance in the urine while the patient is on a diet containing milk.

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SUBSTITUTES FOR COW'S MILK IN INFANT FEEDING*

IT IS HIGHLY essential for the physician to be familiar with the substitutes for cow's milk in patients allergic to this food, particularly during the first six to nine months of life. Over this age, while desirable, such substitutes are not so essential since the protein and other requirements of the infant may be met by feeding other foods, particularly meats, with the mineral and other food factors being given separately. A substitute for butter poses no problem because for cooking a great variety of other fats may be used, and for table purposes (as well as for cooking) hydrogenated soy bean oil is a highly palatable and completely satisfactory butter substitute.† Oleomargarines cannot be used as butter substitutes because most margarines contain a certain percentage of cow's milk solids, as was formerly required by law.

In a discussion of this topic it should be emphasized that the use of cow's milk in infant feeding is of itself a substitute feeding. However, it has been used so long for this purpose that it is regarded by the laity and by most physicians not as a substitute but as a "natural" food. Some years ago I pointed out that the only natural food for the human infant, at least during the first few months of life, is human breast milk, and that despite the fact that she so richly deserves her title of "Foster Mother of the Human Race," the cow, after thousands of years of domestication, still produces milk

* Most of the material for this chapter is taken from an article previously published by the author (10) and reproduced here with permission of the copyright owners.

† This is obtainable commercially under the name of Nuspread, from the Nuspread Foods Company, 2502-6 North Williams Avenue, Portland 12, Oregon. Willow Run Soybean oleomargarine is a similar preparation obtainable from Shedd-Bartush Foods, Inc., 14401 Dexter Boulevard, Detroit 38, Michigan. A kosher oleomargarine of the same nature is manufactured by the Miami Margarine Co., 107 East Pearl St., Cincinnati 2, Ohio, under the name of Mar-Parv.

As a substitute for whipped cream, Rich's Whip Topping may be used. This is manufactured by the Rich Products Corporation, 1145 Niagara St., Buffalo 13, New York.

primarily designed for calves and not for human beings (9). This being the case, any substitute for cow's milk, provided it meets the requirements of the infant satisfactorily, is just as "natural" a food for infants as cow's milk, a concept which is difficult of acceptance both by laymen and by physicians.

Human breast milk would appear to be an ideal substitute for cow's milk as well as a natural food. The chief difficulty is that breast milk is not always available and when available is quite expensive. If produced for allergic infants the mother should be on a special diet, omitting egg, for example. These factors render it impractical for general use.

A hydrolized casein preparation, as Nutramigen,* should theoretically, provide a satisfactory milk substitute. In my experience, its use has been disappointing although many of my colleagues have used it with very good results.† Its taste is unacceptable to older children, diarrhea is frequent, and milk-sensitive babies do not commonly respond favorably. Probably the reason is that infants may be so exquisitely sensitive to milk protein that they will react to it, even when present in such traces that it cannot be detected by the usual chemical or biological tests.

SOY BEAN MILK

In 1917, Osborne and Mendel (18) reported that the soy bean contains all the amino acids necessary for the normal growth and development of the human infant. It is the only member of the vegetable kingdom known to possess this property. Osborne and Mendel's statement is still accepted today with certain reservations as yet unpublished by Albanese** which have to do particularly with a deficiency of methionine, an essential amino acid not yet discovered at the time Osborne and Mendel made their report. However, this objection, Albanese indicates, is more theoretical than real since this deficiency can be compensated by ingestion of additional soy bean above a theoretical minimum (about 4.2 gm. Kg. 24 hr.) which these infants do in the course of satisfying their normal appetites.

* Manufactured by Mead, Johnson and Company, Evansville, Indiana.

† Personal communications.

** Personal communication to the author.

The earliest reference to the use of soy bean in infant feeding is that of Ruräh (24) who did not use it alone but in combination with other foods. Until it was known that a heat-labile trypsin inhibitor occurs in large quantities in soy beans (1, 15) early physiologists were puzzled as to why this complete protein failed to support adequate growth. However, modern methods of preparing soy bean flour inactivate this inhibitor.

In 1929, Tso (27), a Chinese physiologist, stimulated by the report of Osborne and Mendel, and without reference to allergy, sought in the soy bean the protein base for a substitute for breast milk and for cow's milk, the latter apparently quite expensive in China. He succeeded in raising one infant from birth to about the age of six months on a substitute milk made from soy bean without the addition of any protein of animal origin. Not long after the publication of his report I began feeding newborn potentially allergic infants soy bean milk as their sole source of protein. With the exception of the single case described by Tso, five cases of Sternberg and Greenblatt (25) reported in 1951, and my own eighty-eight patients (11), similar experiments have not been published. Sternberg and Greenblatt found that feeding soy bean milk starting at birth throughout the first three months of life had no deleterious effect on the growth and development and blood protein values of these infants.

Although the preparation at home of soy bean milk from soy bean flour is a relatively simple and inexpensive procedure (see Table XXIV) as a substitute food for infants allergic to cow's milk it did not attain any great popularity until Hill and Stuart (13) in 1929 introduced a practical preparation* which became commercially available. Since then a number of others have been developed, the best known of which is Mull-Soy.†

The original Sobee was a powder which made a suspension rather than an emulsion. In 1954, this was replaced by a vastly improved liquid product which contains, in addition to soy bean flour and water, the following ingredients: dextri-maltose (corn and barley malt), soy bean oil, calcium carbonate, sodium chloride, chondrus

* Sobee. Manufactured by Mead, Johnson & Co., Evansville, Indiana.

† Borden Co.

extract, vitamin A palmitate and calciferol. It is theoretically possible, although such cases have not been reported, that certain of these ingredients (dextri-maltose and chondrus extract) might contain enough antigen derived from the parent substances to cause reactions in allergic children. Also, although vitamins rarely cause allergic disturbances and there were found no reports of allergy to vitamin A palmitate or calciferol, it is nevertheless preferable that

TABLE XXIV
PREPARATION OF A HOME MADE SOY BEAN MILK*
INGREDIENTS

Soy Bean Flour (full fat)—This should be processed soy bean flour. The raw flour is unsatisfactory	18 tablespoons
Potato Starch Flour—May also instead use tapioca flour or rice flour or corn starch or arrowroot starch. Care should be taken to use one to whose parent substance the child is believed not to be allergic	3½ teaspoons
Sugar (cane or beet)	5½ teaspoons
Soy Bean Oil (or olive, sesame or corn oil (Mazola))	2 tablespoons
Dicalcium Phosphate (may be purchased from the druggist without a prescription)	1 teaspoon
Table Salt (sodium chloride)	¼ teaspoon
Water to make	32 oz.

All measurements are level; use standard measuring cups, tablespoons and teaspoons. Level off the spoon after filling with the blade of a knife. Sift the soy bean flour once before measuring and do not pack into the cup.

Mix the soy bean flour, sugar and salt in 3½ cups of water (28 oz.). Heat to the boiling point in the top of a double boiler. Add the oil. Mix the starch and dicalcium phosphate in ½ cup of cold water and stir into the mixture. Cook for forty-five minutes in the top of the double boiler stirring occasionally to prevent lumping. If necessary add water to allow for evaporation.

The formula has the approximate caloric equivalent of whole milk; it contains about 30 per cent more protein. The mineral constituents are about the same. The formula was adapted by Dr. Rowe from that of Katherine Bane, M.D., and Miriam Lowenberg.

The addition of a few drops of vanilla or more sugar may make the drink more palatable to older children. Molasses may also be used.

*Slightly modified from Rowe (22).

the formula be as simple as possible and vitamins can be added to the diet at any time and in any form the physician may wish. However, for all practical purposes the liquid Sobee may be regarded as non-allergenic except for those allergic to the soy bean as a food.

Mull-Soy is now supplied in two forms, a liquid (for convenience) and a powder, both of which have the same composition which is somewhat similar to that described above for Sobee except that it contains no vitamins and no potential allergens other than those derived from the soy bean. Either the powder or the liquid may be used as desired. The powder is often well tolerated by infants who suffer

from diarrhea or other gastrointestinal disturbances on the liquid Mull-Soy. A full strength formula is made by mixing equal parts of the liquid Mull-Soy and water or one measure (tablespoon) of the powder to 2 oz. of water.

When first introducing the soy bean milk it is preferable to use a half strength formula until the infant becomes accustomed to it, which usually takes one or two days; then the full strength formula may be used or the formula may be gradually increased to full strength.

On soy bean milk feedings the stools are larger and more frequent than with mammalian milks and this must be explained to the mother. Occasionally, if the stools are too watery the addition of one or two teaspoons of Kaopectate* per bottle as recommended by Stoesser† will correct this. On soy bean milk, or any milk substitute, a common phenomenon which also occurs on the feeding of any food will occasionally occur in early infancy. This is a bowel movement after each feeding. It is not due to the nature of the food but to the fact that the swallowing reflex does not stop with the stomach but goes down through the entire gastrointestinal tract producing an evacuation (gastro-colic reflex). This is most simply treated by giving the infant 5 or 10 drops of paregoric in a teaspoon of water ten minutes before feeding. It usually disappears in a few days.

For older children other soy bean milks may prove more suitable, as Soyolac.** Recipes are commonly provided by the manufacturers for use of the various soy bean milks in agreeable forms in limited diets. A very nice "ice cream" can be made with most of these preparations.

The psychological attitude with which the mother offers the infant, and more particularly the young child, a substitute for the accustomed cow's milk is of the greatest importance. Most of these preparations taste reasonably good to an unprejudiced observer, and whether or not they taste as good as cow's milk is a personal

* Manufactured by the Upjohn Company. Contains citrus pectin; kaolin; bentonite; methyl paraben; saccharin; citric acid, and a synthetic flavor.

† Personal communication to the author.

** Loma Linda Food Company, P.O. Box 388, Mt. Vernon, Ohio.

opinion. If the mother tastes the substitute milk in the presence of the child and makes a disagreeable face or comment in a disparaging tone of voice, the child cannot be expected to take the milk substitute willingly. She should deliberately drink a little in the presence of the child, smile as though very much pleased and say "My, this tastes good." She also should not force the substitute on the child at first but gradually get him accustomed to it.

With the introduction of the soy bean on a large scale into various industries in this country (as pointed out by Duke (4) as long ago as 1934) for use in the manufacture of paint and plastics, and with its introduction as a food, particularly as a protein extender in various kinds of meat preparations and bread, it is to be expected that we will encounter infants who may possibly be allergic to soy bean as well as to cow's milk. This has already occurred (8, 12) and it is, therefore, highly desirable for the physician to be familiar with the other types of cow's milk substitutes which will now be discussed.

GOAT'S MILK

The milk of the goat, an animal which has been aptly termed, as Brenneman comments (2), "the poor man's cow," was in the past very commonly used in the dietary treatment of allergy to cow's milk. As has been discussed above, it is only occasionally more helpful than evaporated cow's milk or boiled whole cow's milk. It is, however, worthy of trial if the infant is allergic to cow's milk and has not responded to any other milk substitutes.

Goat's milk is almost identical in composition to cow's milk, each containing about 3.5 per cent protein, 4 per cent fat, and 5 per cent lactose. It is somewhat higher in minerals, containing about 0.90 per cent as compared with cow's milk, 0.75 per cent. The fat globules of goat's milk are finer and of more uniform size, and there is little tendency for separation of the cream. The curd tension is less than that of cow's milk (2). Fresh goat's milk is usually readily available in the neighborhood of large cities and is occasionally distributed by large dairy companies. Information may often be obtained as to a source of supply from the local board of health. Goat herds maintained with special care and on special diets produce

milk practically free from the characteristic "goaty" odor. However, evaporated goat's milk, used just like evaporated cow's milk, is now readily obtainable at most pharmacies.*

OTHER ANIMAL MILKS

The milk of the ass and of the mare are more like human milk than that of any other animal milk used for food. At one time infants were very successfully fed goat's and ass's milk directly from the udder in large infants' hospitals with very good results (2). Mare's milk has been the subject of a recent study by Kalliala and associates (14) in Helsinki, Finland. They stated that during the period of lactation the amount obtained by the colt from the mother is about 10 to 30 liters daily. The amount of a single feeding is, however, small, the colt compensating for this by nursing frequently, almost hourly, during the day time. The protein content of mare's milk is low, but it contains about 0.5 per cent more than human milk. Qualitatively it resembles human milk in that more than half its protein is readily digestible lactalbumin. The lactose content is intermediate between cow's and human milk. The fat content is low and variable but resembles qualitatively that of human milk as both contain a high percentage of fatty acids. The vitamin content of B₁, B₂, and B₆ is sufficient and it has an excess of Vitamin C as compared with other milks. The mineral content is about the same as human milk, i.e., about half that of cow's milk. However, the amount of calcium and phosphorus, especially calcium, is relatively higher in mare's milk than in human milk and only a little lower than in cow's milk. The buffer capacity of mare's milk is only a little greater than human milk. The digestibility of mare's milk and human milk, as judged by *in vitro* experiments, are just about the same. The stools on mare's milk are relatively soft but are about as alkaline as on cow's milk, whereas the human breast milk stool is commonly acid. Urines on mare's milk are of just about the same

* Myenberg Goat Milk, Distributed by Jackson-Mitchell Pharmaceuticals, Inc., Los Angeles 64, California.

Powdered goat milk may be obtained from Balanced Foods, Inc., 700 Broadway, New York, New York, supplied by the Ditex Food Division, Flotill Products, Inc., Stockton, California.

acidity as on human milk and somewhat less acid than on cow's milk.

Mare's milk would appear to be worth trying in cases of allergy to cow's milk, and it is hoped that, eventually, feeding experiments will be tried on a reasonably large scale in an effort to determine its possible usefulness in this field.

The milk of the reindeer, llama, camel, and water buffalo have been used for feeding children, and legend and fiction state that human infants have been nourished on the milk of wolves and other animals, but no authentic reports on this are available. The same is true of the milk of the anthropoid ape which, as might be expected, is closer in composition to human milk than that of any other species of animal (28). Litchfield, Norton, and Hoffman (16) have published an interesting table of the comparative composition of the milk of several other animals.

Moll (17) used almonds as the protein base for a substitute milk, and other nuts have also been used. Since nuts tend to sensitize readily, I have not used these preparations. Finkelstein (6) published a formula for the use of milk made from poppyseeds which I have used successfully for short-term therapy. Wolpe and Silverstone (29) reported formulae for a series of milk substitutes based on cereals, and Feingold (5) for a milk substitute based on taro, the staple carbohydrate food of Polynesia. These carbohydrate preparations have the disadvantage of not containing sufficient protein so that, after relatively short-term use, the infants develop nutritional edema. I have made limited experiments with human plasma and serum but these substances are impractical for various reasons.*

MEAT BASE MILKS

At present, the best substitute for cow's milk, if soy bean milk is not satisfactory, is prepared by using strained meat as the protein base. The history of the development of this procedure is rather interesting. Rowe (20), in 1931, published formulae using beef and lamb meat juice in milk substitutes. Cohen and associates (3), in

* Unpublished data.

1933, developed a milk substitute in which beef was used as the principal source of protein with other substances added to round out the formula.* To some of these substances infants are readily sensitized and the formula has the great disadvantage of rigidity. Beef, also, is closely related chemically and biologically to cow's milk so that sensitivity to both, though not common, does occur. In 1941, Rowe (21) mentioned homogenized lamb, beef, and beef liver and suggested their use in milk substitutes. I first employed these preparations clinically using a formula kindly supplied by Rowe† at that time. The homogenized meats may be prepared at home, using a Waring blender, as described by Stuart (26), but are now readily available commercially.** Considerable and dramatic success has been experienced first with atopic dermatitis (infantile eczema) apparently due to sensitivity both to cow's milk and soy bean milk (7, 8), and later these meat milks were found extremely valuable in treating severe gastro-intestinal disturbances in early infancy due to sensitivity to cow's milk and sensitivity or intolerance to soy bean milk (12).

The directions for the preparation of meat base milk are given in Table XXV.

The meat milks, which are essentially soups (just as soy bean milk is essentially a bean soup) have a chemical composition very similar to that of cow's milk. The taste is pleasant and they are readily accepted by the infants. Stools are very similar in frequency and appearance to those of cow's milk formula. We have used them successfully as the sole milk substitute during the newborn periods. The meat milks are easy to prepare and, at present, we are using a pork base formula already packed in tins and requiring only the addition of water for immediate use.‡ If this proves practical, the tinned formula will be placed upon the market. I prefer, however, to use lamb since, in my experience, infants show less clinical sensitivity to this than to any other of the commonly

* Formerly marketed by Mead, Johnson and Company, Evansville, Indiana, under the name of Cemac.

† Rowe, A. H.: Personal communication to the author.

** Swift and Company; Gerber (Armour) Company.

‡ Prepared by Swift and Company. Gerber now markets a beef base formula which we have not used yet for reasons mentioned above.

TABLE XXV

SUBSTITUTE FORMULA FOR COW'S MILK CONTAINING STRAINED MEATS*

Strained lamb, pork or beef	1 cup (8 oz.)
Oil (use one of these): Olive, sesame, corn (Mazola)	3½ tablespoons
Ordinary table sugar	2 tablespoons
Starch (use one of these): Potato, tapioca, rice	2½ tablespoons
Calcium carbonate (Get 4 oz. from your druggest—prescription not necessary)	1 teaspoon
Ordinary table salt	½ teaspoon
Water to make a quart (32 oz.)	4 cups

All measurements are level, using standard measuring cups and spoons.

Heat water in the top of a double boiler until the water in the outer boiler starts boiling. Add the salt, sugar and calcium carbonate.

Mix the starch to a paste in ¼ cup of cold water and stir into the water in the top of the double boiler.

Cook mixture for ten minutes in the top of the double boiler stirring constantly to prevent lumping.

Then add the strained meat and oil and make up to one quart, if the total volume is less, with boiled water. Mix thoroughly and cook for ten minutes longer. Bottle and use as formula.

*Slightly modified from Rowe (23) who originated this formula.

used meats except rooster or capon. The male fowl is desirable because it is possible that in the female there is enough egg protein in the tissues to cause reactions in infants exquisitely sensitive to eggwhite. Such cases have been reported in adults by Rinkel, Randolph, and Zeller (19). At present, experiments are under way using whale meat, now readily available in the American market, as the protein base for meat milks. No members of this family are widely used for food in this country so congenital or biogenetic sensitivity to whale meat is not to be expected. The heart of a good sized whale weighs a ton and this high grade protein is now commonly discarded or used for dog food. It should, we believe, form an excellent and inexpensive source of protein for milk substitutes.

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THE ELIMINATION DIET

SKIN TESTS for foods are generally unreliable except for a very few as egg, fish, nuts and seeds. It has been suggested by Ancona and Schumacher (1, 2) that if fresh foods or freshly frozen foods are used the skin tests will be more accurate but exhaustive studies concerning this remain to be reported. Because of the unreliability of cutaneous food tests trial diets are a highly necessary part of the allergist's armamentarium. Such diets should omit all foods to which the patient is, or is suspected of being sensitive clinically, and to which he reacted on skin testing, if any.

Elimination diets of one type or another have probably been used since even before the days of Hippocrates. It is only in recent years, however, that this procedure has been popularized and systematized, particularly as a result of the industry and enthusiasm of Albert H. Rowe (17). In his book may be found instructions for various types of such diets which are particularly suitable for older children and adults. The following elimination diet, which was developed in my practice, has been found highly practical as a basic diet for infants one year of age. Suitable modifications may be made for younger or older children and even adults. This diet, which some pediatricians have called "the rule of two diet," because the ingredients are largely paired, is as follows:

1. Cow's milk and butter substitutes.
2. Cereal: Rice, Barley
3. Vegetables: Carrot, String bean
4. Fruits: Apple, Pear
5. Meats: Chicken (must be capon or rooster), Lamb
6. Vitamins: A, D, and C
7. Miscellaneous: Salt, sugar, water.

For older children another diet indicated by Table XXVI has proven highly satisfactory. It should be modified to suit local conditions.

TABLE XXVI
SPECIAL ELIMINATION DIET
Diet Instructions

For a period of two weeks the diet is to be strictly limited to the foods listed below. You may have any combination of the foods here listed and as much as you want of them but you may not have any other foods unless they are made up only of the ingredients listed below. If there is any question about this, the food may not be used. The answer to the question, "May I have such and such a food?" is—if it is not here listed it may not be used. Be sure to have everything prepared before starting the diet.

I. Beverage: Tea

Soyalac (all purpose, unflavored). This is manufactured by the Loma Linda Food Co., Box 388, Mt. Vernon, Ohio. It may be used in most instances as a substitute for cow's milk. For a butter substitute use Nuspread, or Willow Run Soybean Oleomargarine.^o

II. Meats: Lamb; chicken (must be capon or rooster).

III. Cereals: Ry-krisp (Ralston-Purina Co.)—may be used as a cracker or ground up in a meat grinder and used as a breakfast cereal.

*†Cellu Rice Wafers
Quaker Puffed Rice
Minute Rice (General Foods)
Plain boiled rice.

The cereals may be served with Soyalac; the juice of the permitted fruits or vegetables; maple syrup; or honey (light).

IV. Fruits: Apple; pear; raisin; pineapple.

V. Vegetables: Carrot; string bean; lettuce; sweet potato.

VI. Miscellaneous: Water; sugar; salt; vinegar (apple cider only); apple jelly; cranberry; honey (light); maple sugar; maple syrup; *†Soy Nuts—these are very similar in taste and appearance to salted peanuts and are useful as a "filler" between meals.

* May be obtained at the Healthful Diet Shoppe, 200 Monroe Ave., Rochester 7, N. Y. Phone: Baker 4674.

^o Manufactured by Shedd-Bartush Foods, Inc., 14401 Dexter Blvd., Detroit 33, Mich.

† Manufactured by the Chicago Dietetic Supply House, Inc., 1750 W. VanBuren St., Chicago 12, Ill.

Report to this office (Monroe 0019) after you have been on the diet for a week but make no changes in the diet without specific instructions. It is important to adhere to the letter of the diet as this may be the only possible way of solving your problem. If the diet is successful it will gradually be enlarged in a manner in which you will be directed.

Substitutes for cow's milk have been discussed in Chapter 62 and need no further elaboration here.

In my experience, clinical allergy to cereal, except to wheat, in infants and young children, has not been very common. It is important to remember, however, that all the cereal grains: wheat, rye, rice, oat, barley and corn, are all genetically related in that they are all modified grass seeds and a person exquisitely sensitive to one may be, though not necessarily, sensitive to all. It is highly probable that the kind of clinical sensitivity to cereal grains will depend to a degree upon the part of the world in which the patient lives. In the temperate zone wheat is the staple cereal; in colder climates, as in Scandinavia, rye products are best liked; in Mexico corn, and in

tropical and subtropical countries, rice. In my practice sensitivity to rice and barley rarely occurs. More frequent is sensitivity to corn and oat and most frequently to wheat and rye. Slobody, Untracht, and Herzmark (18) found no children sensitive to cooked rice. They assumed that the heating of rice in the presence of moisture renders it non-allergenic, as suggested by the work of Ratner and Gruehl (14). While such cooking tends to make cereals and other foods definitely less allergenic, the process by no means makes these foods perfectly innocuous from the allergenic standpoint. For example, the author, as well as many other pediatricians, has seen wheat sensitive infants who have developed rashes from the wheat in Pabulum Mixed Cereal* which is an excellent thoroughly pre-cooked cereal. Such a patient is illustrated in Figure 13. This boy's skin could be completely cleared by a wheat free diet. However, the ingestion of Pabulum Mixed Cereal or any other food containing wheat would cause an eczematous rash to appear in the flexures of his knees and elsewhere within less than twenty-four hours after ingestion.

Pure rice and barley cereals, as well as other single grain cereals, and now readily available, in most cases in some variety, on the market, except for rye. However, Ry-Krisp wafers† may be ground up in a meat chopper and used as a pure rye cereal. By consulting the references in Table XXVII many additions may be made to the above diet to make it more palatable, as for example, the rice or barley or soy-bean wafers containing only the single food plus hydrogenated soy bean oil and suitable hypo-allergic excipients and sweeteners.

Buckwheat, which would appear to be a good substitute for the commonly used cereal grains, is botanically not a cereal but is a member of the rhubarb family. It is not a practical food for allergic individuals because sensitivity to buckwheat is easily acquired and very severe reactions may occur in such sensitized individuals.

The fruits and vegetables in the diet under discussion require little comment. These were originally used because they did not appear (except for carrot) in a table of positive skin reactions in 200 children as reported by Hill (12) in 1933. Clinical experience since

* Mead, Johnson and Company.

† Ralston, Purina Company.

TABLE XXVII

SOURCES OF SPECIAL INFORMATION WITH REGARD TO DIETS AND RECIPES*

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- Good Housekeeping Institute, 57 St. at 8th Ave., New York 19, N. Y. *Herbs for Allergies*. Price \$0.10.
- Chicago Dietetic Supply House, Inc., 1750 W. Van Buren St., Chicago 12, Ill. Allergy Diet Foods. For Use in Wheat-Free, Egg-Free and Milk-Free Diets. Copies supplied gratis.
- Quaker Oats Co., 223 W. Wacker Blvd., Chicago, Ill. Allergy Recipes. Copies supplied gratis.
- Ditex Foods, 918 Armitage Ave., Chicago 14, Ill. They have some fine special items for use on allergy restricted diets.
- Fruit Dispatch Co., Pier 3, North River, New York, N. Y. Supply gratis a very convenient recipe for a banana rye bread for persons allergic to eggs, wheat and milk.
- Kannengiesser & Co., Inc., 76 Ninth Ave., New York 11, N. Y. Supplies gratis recipes for foods containing banana on allergy restricted diets.
- Borden Co., Prescription Products Division, 350 Madison Ave., New York 17, N. Y. Supplies gratis book of recipes for using Mull-Soy on milk-free diets.
- Aderle, Edna M.: *Wheat Free Recipes for Allergy*. 404 Lincoln St., Rhineland, Wis. Price \$0.50.

* Modified from Dees, S. C. (5).

then has confirmed the validity of the use of these particular ingredients in elimination diets at this age.

If a child will not take the milk substitute on the elimination diet it is important to administer sufficient calcium and phosphorus in suitable amounts in an acceptable vehicle.*

VITAMINS IN THE ELIMINATION DIET

For short-term trial therapy, as for a period of one or two weeks, if a child is in reasonably good condition it is not necessary to fortify the diet with vitamins. However, if the trial diets are to be more prolonged it is advisable to see that the requirements for vitamins are met. Most commonly this can be done by providing some simple preparation containing A, C, and D. The requirements for A and D are usually satisfied by prescribing some form of cod liver oil.

* Dynacal (McNeil) is a convenient preparation, each teaspoon or tablet of which contains the calcium and phosphorus equivalent of 7 oz. of cow's milk.

Fortunately, sensitivity to cod liver oil preparations is quite uncommon. Balyeat and Bowen (3) reported four children between the ages of four and six years who developed urticaria, or vomiting, or diarrhea or eczema when fed cod liver oil. Hoffmann and Rattner (13) reported two children ages eighteen and twenty-two months respectively who developed eczema from cod liver oil. Both of these children were clinically sensitive to the ingestion of fish.

It is possible that sensitivity assumed to be due to cod liver oil may not occur because of sensitivity to cod fish *per se* but because of sensitivity to some product which is developed in the cod liver oil in the process of purification. This was suggested by an experience with an infant one and a half years of age who, when tested by the scratch method with codfish, reacted immediately with the development of a wheal which reached the size of 5 cm. before the testing material could be wiped off of the skin. The mother was immediately queried as to why she had not stated that fish disagreed with this child when, in taking her history, she was specifically asked if any particular food disagreed with the infant. She replied that the child was so sensitive to fish of all kinds that she did not dare even to bring a fish into the house as the odor alone would cause the child to have asthma. She had not thought of fish disagreement when the question of food disagreements came up because it had been so long since the child had been exposed to fish.

This is a common type of omission which may occur in history taking when one inquires only if there are any known food disagreements, rather than giving the mother a food list to check or asking her specifically concerning the child's reactions to any given foods, as has been discussed under history taking. This child was then scratch tested at the same visit using samples of a half a dozen of the various kinds of cod liver oil preparations. She reacted to none of these. This suggests that in the course of processing cod liver oil this may be rendered non-allergenic so far as fish is concerned indicating that if reactions do occur to such products they may in some instances be due to changes which have taken place in the oil as a result of processing. Nevertheless, in order to avoid possible difficulty from this source it is my custom to use a substitute for cod liver oil to which no allergic reactions have been reported as yet. For this purpose there

are now many synthetic water soluble or miscible A, C, and D or A and D preparations available.

VITAMIN C

To provide an adequate non-allergenic source of Vitamin C one may use the "Ce-Vi-Sol" of Mead, Johnson and Company, which consists of crystalline ascorbic acid dissolved in glycerin, or the "Cecon" of the Abbott Laboratories, which contains crystalline ascorbic acid dissolved in propylene glycol. Crystalline ascorbic acid may also be prescribed in capsules.

Di Sant'Agnese and Larkin (7) found Vitamin A absorption capacity impaired in four cases of intractable infantile eczema. Each of these was characterized by: (1) retarded development; (2) malnutrition; (3) severe generalized eczema; (4) marked lymphadenopathy; (5) high blood eosinophilia (25 to 35 per cent); (6) frequent, severe respiratory infections, and (7) refractiveness to local and dietetic treatment. Vitamin A blood levels were determined before and after the ingestion of oleum percomorphum. The authors suggested that respiratory infections and malnutrition when observed in infantile eczema may be due to vitamin A deficiency resulting from a defect in intestinal absorption. Should this problem be encountered it could probably be adequately met by the feeding of one of the highly potent Vitamin A preparations now available.

Harris and Gay (11) fed twenty unselected infants with eczema a Vitamin B complex preparation. An immediate improvement manifested by a decrease in pruritis and a tendency toward healing was noted in eighteen cases. However, in the final analysis, only two healed completely, eleven improved, and seven showed no change. In my experience the procedure has been consistently disappointing.

Wetzel and associates (21) reported one child whose eczema was apparently greatly improved by the administration of Vitamin B₁₂. Dieterich (6) reported in some detail on a two-year-old child who had eczema since infancy who did not respond to the usual methods of treatment which were discontinued and the child given 10 micrograms of Vitamin B₁₂ daily. After two weeks there was a complete remission of the eczema. The same dose was continued for another two weeks and then reduced to 7.5 micrograms daily. The remission had persisted up until the time of the report.

With the possible exception of the work by Di Sant'Agnese and

Larkin, which has not yet been confirmed, there appears to be no unequivocal evidence that vitamins are of any greater importance to the child with allergic disease than to the normal child, or that allergic diseases are in any way favorably influenced by the administration of any presently known vitamins. The use of vitamins as therapeutic agents in allergic disease has been characterized by more enthusiasm than sense. Together with Dam (8) I have the rather odd distinction of being the first to describe the use of a new vitamin in an allergic disease (Vitamin E in pollinosis) without reporting favorable results.

UNSATURATED FATTY ACIDS AND ATOPIC DERMATITIS

Hansen (9) has contributed some studies of fundamental, though not highly practical, importance concerning the metabolism of the eczematous child. He stated that fatty acids containing two or more double bonds are not synthesized by the body, and certain of these, linoleic acid (C 18 with two double bonds), and arachidonic acid (C 20 with four double bonds) are known in nutrition as the essential fatty acids. In about four-fifths of eczematous infants under two years of age and a little over one-half of adult patients with eczema, the serum iodine numbers were found to be below the normal range. Hanson and associates (10) were able to raise the iodine number of fatty acids in the serum of dogs by feeding lard. The same procedure has been effectively applied to infants with eczema. The lard is spread on crackers or mixed with other foods and appears to be taken well by the patient. It is given in teaspoon or tablespoon quantities once or several times a day as tolerated. A therapeutic trial should comprise a period of about two months or so using 1 to 2 oz. a day.

Stoesser (19) in a series of severely eczematous infants noted blood iodine numbers averaging 71, which is much below the normal. These infants were fed soy bean milk to which had been added 4 per cent soy bean oil to increase the amount of unsaturated fatty acids. In a period of three or four weeks the iodine numbers rose to an average of 118 and this was associated with favorable response to external therapy. In a control group there was little change in the iodine number. Stoesser felt that these observations confirmed others previously made (20) to the effect that during acute infections of the

respiratory tract in infants with eczema, the skin showed temporary improvement at the onset of the fever, but was much worse thereafter. He attributed this to the observations that early in an acute infection there is a sudden flow of unsaturated fatty acids into the blood stream which is followed by a fall to abnormally low levels.

Obviously, basic work of this nature in eczema is much to be encouraged. However, the difficulties of obtaining satisfactory controls in a disease which is often self-limited and always subject to unpredictable exacerbations and remissions and which at the same time may require other measures than dietary for its amelioration are self-evident. An interesting possible explanation as to why the feeding of unsaturated fatty acids to infants with eczema has not attained any significant popularity is the fact that by the time Hansen's work became generally known, the majority of infants with this disease were being fed soy bean milk which is reasonably rich in these acids. These perhaps have a critical level as far as the improvement of atopic dermatitis is concerned which is not influenced by the further addition of unsaturated fatty acids to the diet.

MANAGEMENT OF THE ELIMINATION DIET

The mother is told that the child may have as much as desired of any food listed on the diet and also may have any combination of these foods. The answer to the invariable question, "Can the child have this or that?" is, that if it is not specifically listed the child cannot have that food. The mother must be educated to become a persistent label reader. If she is in any doubt as to what any particular store-purchased food contains, then that food should not be used. No changes of any kind are to be made in the diet without consulting the physician. He should see the child, or discuss the patient with the mother over the telephone at least every four or five days.

Generally speaking, if the elimination diet is successful, the allergic condition usually shows marked improvement within forty-eight hours, although at times a week may be required. The child should be kept on the diet until the skin is perfectly clear. New foods may then be added at the rate of one every four or five days. The guidance of the mother should be sought in adding these new foods as she knows what the child likes and it is important to make the diet as palatable as possible. The last foods to be added are

those which are the most likely to cause trouble, i.e., wheat, milk, and egg, and they should be added in that order.

Wheat should first be added in the form of a pure wheat cereal which contains no other potential allergen. Puffed wheat is one of the best of these, although other pure wheat cereals as Shredded Wheat and Ralston's may be used. Matzos, which is pure wheat, may also be used as a cracker or bread substitute. If the wheat agrees with the child, the mother may then cautiously try thin toast (melba toast) made from bread which does not contain milk solids or egg. Bread purchased at a reliable kosher bakery will not contain milk or milk products. However, egg powder or other forms of egg are sometimes used in bread making and the baker must be consulted specifically regarding this. If the thin toast is tolerated, then untoasted bread may be tried next.

The next to the last food to be added is milk, and one may first start with butter, then cream, then cottage cheese, and finally evaporated milk, and, if this agrees, whole milk. Each cheese (other than cottage cheese) must be tested as an individual food. This is because the mold, which gives the cheese its distinctive flavor, may act as an allergen.

As a rule, the last food to be added in the case of children, especially those with atopic dermatitis, is egg. One should start with $\frac{1}{4}$ of a hardboiled egg yolk three times a week. If this agrees the amount is increased by $\frac{1}{4}$ of a yolk per week until the child gets a whole hardboiled yolk three times a week. Then, hardboiled egg-white should be gradually added until the child gets a whole egg three times a week. If this agrees then egg in other forms may be tried. For a few months egg should not be given oftener than three times a week, even if it appears to agree perfectly.

Occasionally an elimination diet will work in reverse. That is to say, the child will get worse instead of better while on the diet. This usually indicates that the child is sensitive to one of the included foods but, because there are so few of these, the culprit is usually found with ease.

THE ROTARY DIVERSIFIED DIET

It is also occasionally discovered that when a new food is added to the diet it may be well tolerated for a varying period, say for a

few days or a week, and it will then disagree with the child. This may happen with a number of the foods as they are added to the diet. In such cases it is necessary, in order to prepare a satisfactory diet, to use these foods in rotation with others which may disagree in a similar manner. This type of diet is known as "rotary diversified diet" and has been particularly developed and advocated by Rinkel (15).

The general procedure which Rinkel advocates is that whenever a patient is proved sensitive to a food, it is omitted until tolerance develops, usually a matter of three to eighteen months. The food is checked for tolerance at three months and if a reaction occurs it is rechecked at nine months.

Another test is made at the end of a year and if there is still a reaction, a final test is made at eighteen months. If this test is followed by symptoms, it is best to consider the food as a permanent food allergy and discard it. If the food fails to produce symptoms, it is used once a day at five-day intervals for six feedings. If symptoms do not occur, the food may be used once every three days and after three months every two days. There are very few foods beyond infancy and early childhood which have been allergens that can be used after tolerance has been achieved by elimination at intervals of less than once in three days. However, even when a food is used only once in three days the patient may become resensitized. These allergies are insidious and difficult of detection and when the offending food is discovered, if used again the interval must not be closer than once in six days.

A food which causes eczema in a baby does not necessarily cause asthma in childhood if the patient has become asthmatic. There is no food which, after tolerance has been obtained, may be replaced in the diet using the same frequency as before sensitization was proved, without the allergy recurring. This, however, in my experience, is not necessarily true in infancy and childhood as will be mentioned shortly. When the diet fails to produce the desired result, individual food testing is indicated. The directions for this are stated in Table XXVIII (16).

There are certain foods to which, if an individual becomes sensitive to them, sensitivity is very likely to persist throughout life. This is particularly true of fish, nuts of all kinds, and coconut. There is no

TABLE XXVIII
INDIVIDUAL FOOD TEST*

1. The food should be used at least once daily every other day for at least two weeks preceding preparation for the test.
2. The food should be avoided exactly four days and tested on the fifth day.
3. Patients should take neither food nor liquid nourishment for five hours preceding the feeding test.
4. All medicine is to be avoided for four hours.
5. Drinking water and smoking to be avoided for three hours.
6. Use an average portion which is to be eaten within five minutes time. Should the food fail to be followed by definite symptoms at the end of one hour repeat the feeding using one-half or one-fourth portion.

Tests are preferably started at noon rather than at breakfast.

Do not serve ice cold food or excessively hot food.

No sweetening agents other than pure cane sugar are to be used.

The patient should be kept in a constant environmental status, i.e., avoiding exercise, animated conversation, drafts and change in posture. The usual position is resting quietly in a comfortable chair, preferably reading.

Except for the food tested, which usually may be taken as desired, the meals for the remainder of the day of the test should include only those foods taken the previous day.

† Blood Counts: Take after thirty-minute rest period; then again at twenty, forty, and sixty minutes after the initial ingestion of the food. Use the same pipette.

The term "leucopenia" implies a diminution of leucocytes of at least 10 per cent greater, in at least one or more of the three post-ingestive determinations. Numerically this most commonly means a decrease of at least 1,000 cells. Commonly, but by no means invariably, the onset of clinical symptoms occurs coincidentally with the fall in leucocyte level.

Wheat: Cooked Ralston salted to taste.

Corn: Cooked corn meal salted to taste and sweetened with dextrose or dark Karo syrup.

Eggs: Two hard or soft boiled.

Milk: One quart, preferably the brand used at home. Do not bring in paper cup.

Potato: One large baked or one medium and one small baked.

Oranges: Two medium or 8 oz. of pure, fresh orange juice.

* Modified from Rinkel, Randolph, and Zeller (16).

† While of considerable interest, the clinical reaction to the food is the item of most importance and in my practice these blood studies are commonly omitted.

satisfactory way of treating this kind of food allergy except by avoidance. Attempts at hyposensitization by oral feeding of gradually increasing doses of the allergen or by hypodermic injection of the allergen in gradually increasing amounts is, in my experience, useless and dangerous and should never be used. The good results reported in this procedure by Brandenburg and Wilander (4) are completely at variance with common experience in this country.

As regards those food sensitivities which may be lost spontaneously, there are no definite statistics as to exactly when this might happen. In my experience practically all children who are going to lose their sensitivity to cow's milk do so within the course of a year. Egg may take longer, two or three years, except in very early infancy (age three to four months) when sensitivity may be lost over a

six- to nine-month period. Sensitivity to other foods on avoidance is generally lost in less than a year. In the case of some foods, such as fish and nuts, tolerance may never be acquired.

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CHAPTER 64

CLIMATE AND ALTITUDE

ALTHOUGH the relationship of climate to allergic disease is of great importance and is a frequent topic of conversation between the physician and the patient, there has been very little written on this subject, particularly with respect to children. Schutzbank (6), who practices in Tucson, Arizona, stated that there is as yet no definite agreement as to what produces improvement when a patient changes his climatic environment. When a patient is promptly relieved of allergic disease after a change of climate, it is probable that he left behind something to which he was allergic. This might be a food, an environmental factor or some psychic factor which acted as a trigger mechanism for initiating an allergic attack.

It is very necessary to distinguish between the effects of a change of climate and the effects of separating an asthmatic child from his home environment and parents. Peshkin* has concluded that there is a group comprising about 10 per cent of all asthmatic children in which the child, living at home, will not obtain relief by the orthodox methods of allergic and psychiatric study. He felt that the only method for giving these children relief was to take them away from their homes and their parents and place them in a warm emotional climate in a group setting with appropriate father and mother substitutes. This procedure Peshkin has termed "parentectomy." This was difficult to accomplish both from the practical and economic standpoints. The problem was solved by the development of the Jewish National Home for Asthmatic Children in Denver, of which Dr. Peshkin is the chief medical consultant. This is a non-sectarian home under Jewish auspices to which suitable asthmatic children may be admitted without regard to the financial status of the parents. The details of the home and its operation have been described

* Personal communication to the author.

in lay terms by Rosenfeld (4).^{*} At present Dr. Peshkin is in the process of analyzing the vast amount of data which has been collected with respect to the Home over the past eight or nine years with particular reference to children from metropolitan New York. A preliminary survey has indicated[†] that about 70 per cent of the children discharged after not less than a two-year period at the home as free or relatively free from asthma, have remained in that condition after returning to their homes after a period of one or more years.

Although the climate of Denver is relatively mild and dry as compared with many other cities in the United States, nevertheless there is an abundance of allergic disease in Denver and it is quite evident that climate alone is only one factor in the beneficial effects obtained with asthmatic children at the Jewish National Home for Asthmatic Children.

The Southwestern United States has always been a favorite Mecca for asthmatics wishing to experiment with a change of climate. Many go to Tucson which, Schutzbank (6) states has an elevation of 2,400 feet above sea level with a usually stable barometric pressure, little rainfall, very low average humidity, and a high mean temperature with an abundance of sunshine. However, because of the climate the pollinating season lasts nine to ten months, and because of the dryness there is much dust which may cause trouble for asthmatics by causing inspissation of the mucus and this forces many such patients to leave for a less dry climate. Patients with respiratory infections and frank bacterial asthma usually do well. Schutzbank stated that, in almost half of those relieved, the improvement could be attributed to the avoidance of psychosomatic influences. This is not to imply that in these cases sensitivity to various allergens played no part, as the psychosomatic influences were probably responsible for lowering the threshold of tolerance to such allergens. Patients not helped were those with chronic infection of the respiratory tract, such as sinusitis, bronchitis or bronchiectasis not amenable to treatment, patients who had had

^{*} A reprint of this article and other information may be obtained on request by writing the Jewish National Home for Asthmatic Children, 3447 West 19th Avenue, Denver 4, Colorado.

[†] Personal communication from Dr. Peshkin. To be published.

extensive surgical treatment, and, as might be expected, other failures were due in part to complications as emphysema, bronchitis or cardiac disease. Schutzbank concluded that too many patients are pathetically disillusioned and put to great financial hardship by needlessly being sent away for climatotherapy. Older patients and those with chronic infections of the respiratory tract are often greatly helped by moving to a warm, dry climate. Those aggravated by cold, high humidity, storminess and rain may be benefited by climatotherapy. Persons sensitive to pollen and dust should be carefully considered before they are advised to change to the southwestern United States for any allergic disorder. When a patient is advised to change his climatic environment he should be told that it may take as long as a year or more to give the desired improvement and that it is advisable to receive or continue recognized methods of treatment and not to depend upon climate alone to effect a magic cure.

Criep and Hammond (1) have reported on western Pennsylvania and the adjacent portions of West Virginia and part of Ohio with Pittsburgh as a center. This zone is located in a "storm belt" which causes at times low barometric pressures, followed characteristically by high pressures, clear skies and low temperatures. In spite of this the climate is generally temperate although there are a considerable number of cold days, about a hundred during the year with the temperature below the freezing point, with a range of 32°C. (0 F.) to 38°C. (100°F.), the mean daily range being about 7.6°C. (20 F.). There is abundant sunshine, many cloudless days, and generally mild winds. Humidity levels tend to be high but are not striking in any direction. Air contamination includes industrial irritants and smoke. The pollinating period is from February to October.

Harsh (2) has reported a direct correlation between humidity and house dust sensitivity, a fundamental and important observation if verified. This would be of great significance with respect to climate as patients with a high degree of sensitivity to house dust would not obtain relief by moving to a humid climate.

Rowe (5) has discussed climate as related to food allergy, stating that such allergy may become less active or even absent during the summer months and increase during the winter months. Food allergy may also be activated in maritime areas near the ocean as ob-

served in northern California and may disappear or decrease inland even five to ten miles away from the salt water. All food sensitive patients are not affected in this manner and seasonal and geographic effects may both occur in varying degrees in the same individual or either one may act alone without any evident effect on the other.

Marks (3) has reviewed the literature dealing with the effect of the climate of Florida on allergy and studied this subject with special reference to allergic children. He concluded that most allergic children who came to Florida improved to a point more or less permanently but that the degree of improvement depended upon the type of existing allergy. The critical period of change was generally considered to be two or three years. If relapse did not occur after this period of residence in Florida, further improvement in the respiratory condition could well be expected. It was also observed, however, that many children, though not having allergic manifestations in the North, developed respiratory allergic symptoms when the family moved to Florida. When southern Florida favored improvement it was largely because its climate reduced the incidence of upper respiratory tract infections and afforded freedom from northern pollinosis. In southeastern Florida, house dust is probably the all-important allergen. Contrary to the observations of other workers, Marks was not convinced that molds in southeastern Florida are of unusual significance as an etiological factor in childhood allergy. Like all others who have written in this field Marks stressed that every child must be managed on an individual basis, every aspect of the problem, including psychogenic factors, being thoroughly considered.

Smith and Garrett (7), of El Paso, Texas, have had the opportunity to study many patients with chronic skin diseases, particularly chronic atopic dermatitis (eczema), who have migrated to that part of the country from colder and more humid regions to take advantage of the sunshine and the warm, dry air. They concluded that it would be a mistake to attribute the improvement of these patients to climactic influences alone and to leave the impression that climato-therapy without attention to the other factors involved is necessarily followed by a rapid return to health. Change of environment and change of climate appear to be only two of the factors which may be beneficial to these patients. Change of emotional environment, more

rest and relaxation, and slower tempo of life are equally important. In spite of the climate of the Southwest, as well as other climates usually considered favorable, this group of dermatoses, when they develop in these portions of the country, remain a problem just as elsewhere unless the other factors receive adequate attention.

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THE RELATIONSHIP OF ALTITUDE TO ALLERGIC MANIFESTATIONS

It is a common belief that high altitudes favorably influence allergic diseases. That this is not true, particularly with children, was first reported by Dr. Julia Baker (1), an American pediatrician practicing in Mexico City (altitude 7,325 feet). She has accumulated evidence indicating that allergic reactions are more common there than at lower altitudes. From this she has deduced that (1) mountain sickness, some of the symptoms of which are the same as those of allergic reactions, may possibly be explained on an allergic basis, and (2) the higher the altitude, the more allergy will be encountered. In this connection it is interesting that the highest city in the United States is Denver, Colorado (elevation 5,280 feet), and that the inhabitants of that city have their allergic problems just as elsewhere in this country.

The symptoms of mountain sickness to which Baker referred as

* Since this manuscript was submitted for publication, the first book devoted to local allergic problems of the United States and neighboring countries has appeared: Samter, M. and Durham, O. C.: *Regional Allergy of the United States, Canada, Mexico and Cuba*; Springfield, Ill.; Charles C Thomas, Publisher, 1955.

similar to those of allergy are nausea, vomiting, depression, both mental and physical, and diarrhea. As an explanation for the increased occurrence of allergy at higher altitudes Baker suggested that the anoxia experienced in an altitude such as Mexico City may result in increased permeability of the gastrointestinal tract with a greater accumulation and absorption of protein products than at lower levels. Low pressure and anoxemia are definitely the basic causes of mountain sickness and this definitely modifies physiological functions. Baker stated that she had been able to find only one reference in the available literature indicating an influence of altitude on allergic manifestations. This is a paper by Kopaczewski and Marczewski (5) on anaphylactic shock, recording the induction of convulsions in guinea pigs sensitized to beef serum albumin one month previously. These animals, together with normal controls, were placed in a pneumatic caisson and the atmospheric pressure depressed at a rate corresponding to a rise in air of 1000 meters per minute until the equivalent of 10,000 meters (32,500 feet) was reached. At this point all sensitized animals were in convulsions (with the exception of those which had gone into convulsions earlier) and a slow descent was made. At 6,000 meters (19,500 feet) (in three minutes) all the animals recovered, the only symptom persisting was a lower temperature. Controls remained normal except for a slight lowering of temperature. These experiments were confirmed by the U. S. Army Air Force during the recent war, according to a personal communication from Dr. Baker.

Loss of weight characteristically accompanies the anoxia of high altitudes and the reasons for this have been assumed to be loss of appetite, restlessness, diarrhea, etc. In persons coming to Mexico City a period of about two weeks is usually required for the effect to accumulate and become manifest in symptoms.

Baker (3) in a series of 1,000 unselected children found that 509, or approximately 50 per cent, had allergic symptoms. She presented evidence that many children with manifestations of allergy in the United States experience exacerbations when taken to Mexico City, and many children without allergic symptoms at lower altitudes develop allergic diseases in Mexico City, particularly in the case of children where there is a family history of allergy. In these instances the allergic symptoms are unrelated to the race of the

patient and are commonly due to foods. While hives are the most clear-cut symptoms, all other allergic reactions may occur, particularly gastrointestinal and respiratory. Baker reported the case of a girl who, starting at the age of four months, would have hives associated with loose bowel movements in Mexico City. The symptoms always disappeared at lower altitudes, to reappear whenever she returned to Mexico City. This difficulty could be avoided if cow's milk, raisins, and bacon were omitted from the diet. These foods were well tolerated at lower altitudes except when taken in excess. Another girl, first seen at the age of four months, developed numerous allergic manifestations on coming to Mexico City, particularly urticaria and allergic rhinitis. These could be controlled by elimination diets, milk being the principal offender.

Baker has found that skin tests are not of great value in these cases. Symptoms are generally controlled by eliminating the foods which most commonly cause trouble in Mexico City—egg, chocolate, orange, milk, and wheat. With the elimination of the offending foods for a considerable period, sensitivity is generally lost but builds up again on resumption of these foods, usually in a fairly constant time. In Baker's practice, allergic reactions are as common as infections, except in the very poor groups. Babies begin to develop food intolerance at seven to eight months starting with diarrhea followed by vomiting, allergic rhinitis and bronchitis. Urticaria and eczema are also common. Mexican physicians call the condition "altitude urticaria" and state that the babies will outgrow this. In the treatment of allergies to foods at high altitudes Baker (4) uses a variety of rotary diets in a system of feeding which may be used not only at high altitudes but with allergic children in any locality and with children of allergic families to prevent the development of food allergies and as a test diet to determine if anorexia or other unexplained symptoms may be due to sub-clinical allergy. She dispenses with rigidly fixed diet schedules and instead gives the mother printed instructions listing foods which may be used for two successive days or better alternately every three days. For example, cereals are listed as oatmeal, cornmeal mush, rice flour gruel, or cream of rice, barley cereal, and tapioca. She uses no mixed cereal preparations. The same plan is effective for fruits and vegetables, and as there is more variety of these products it is easier to vary

them. Orange juice is not given at all in the early months, ascorbic acid being substituted. When orange juice is begun, it is given alternating with tomato juice and other fruit juices and ascorbic acid is continued. Cereals are started at three months, cooked fruits at four months, vegetables at five months, and meat at five or six months. Lamb, beef, chicken, and liver are alternated. Tuna fish and sardines may be well tolerated and given once a week. Eggs are not given until the end of the first year, and then only a hard boiled yolk once or twice a week. Wheat is not given as a cereal gruel, but at about nine or ten months of age is given as toast once or twice a week.

Milk sensitivity is the main problem because of the lack of adequate substitutes for milk. Babies who have trouble with milk can sometimes be fed for quite a while on three days of Nutramigin* alternating with three days on soy bean milk. Meat base milks may also be used.

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* Mead, Johnson & Co.

THE ALLERGIC CHILD IN CAMP*

AN IMPORTANT consideration in the treatment of any chronic disease, and this is especially true in childhood, is the attempt to prevent the patient from developing a sense of invalidism. The more a child can enjoy activities common to other children of his age, the healthier and happier he will be. Camps especially for diabetic children are highly successful and have contributed to our knowledge of diabetes in childhood. Camps especially for children suffering from allergic disease have not as yet been established but with the advances which allergy is now making as a specialty, it is perhaps time to consider the desirability of organizing such camps. Meantime, every summer all physicians caring for children are confronted with the problem of what to do with their allergic young patients who wish to go to camp.

One of the primary considerations for such a camp is that there should be a resident physician in attendance. Previous experience in treating allergic children is highly desirable as a qualification for the camp physician, but cannot be insisted upon. Many camps employ a nurse for routine care of campers and depend upon a physician in a neighboring town in case of necessity. Where this is the case, the practicality of sending a child to such a camp must be seriously considered. Not all allergic children, because of the nature and severity of their illness, should be permitted to go to camp, even if the parents are willing. Which child should or should not go is, in every case, an individual problem to be decided by consultation between the parents and the physician.

A child on a highly restricted diet should not be sent to camp because the difficulties inherent in carrying out such diets are accentuated by the increased appetite usually associated with camp life

* The material for this chapter has been taken largely from a previous publication by the author (3) on the same subject and is here reproduced with permission of the copyright owners.

and activities. Even if the food allergy is associated with the ingestion of easily avoidable foods, such as nuts or berries, the responsibility for avoiding these cannot be assumed by the camp management. In the case of a very cooperative child it is a reasonable risk, but otherwise not.

Before going to camp any child, and particularly the allergic child, should have a thorough physical examination by a physician. Many parents resent having their child examined when the child feels well, but most do not resent having a well child thoroughly examined once a year. It is highly advantageous for the physician to educate the parents of his camp age children to utilize the camp examination as the child's yearly physical examination. An important part of this examination is a check on whether or not the child has had the prophylactic injections now considered desirable and has had a negative Schick test and a tuberculin test. Probably the most important of the prophylactic injections is that of tetanus toxoid. While there is no simple, practical test to determine whether or not these injections have been effective in any individual case, experience indicates that the procedure is highly effective. Tetanus has practically been eliminated from our armed forces by immunization with toxoid, and no better evidence could be given. There are also, in my experience, no contraindications to administering tetanus toxoid to children, whether allergic or not. In the case of highly allergic children, a preliminary test dose of 0.10 cc. of toxoid subcutaneously is sometimes administered and the reaction noted, but since the report of Long (5), indicating that reactions to toxoid in the Army are less than one in 10,000, even this precaution is commonly omitted. Since Long's publication, improvements in the manufacture of tetanus toxoid have rendered the reactions which used to occur in pediatric practice rather infrequently still less frequent. In the rare event that a child should give a severe reaction to tetanus toxoid, it may be given in smaller doses (see Chap. 66). If, by some chance, a child has not been immunized against tetanus by means of toxoid before he goes to camp, he may at least be given the first dose and arrangements made with the camp physician to administer the succeeding doses. In the event that this is not done, and an indication for the use of tetanus antitoxin arises, the camp physician should be instructed to use bovine tetanus antitoxin (2)

instead of the usual horse serum antitoxin, and if this is not available, or if the child is beef or milk sensitive, a despeciated antitoxin (see Chapter 66).

The problem of protection against typhoid fever is the same for the allergic as for the non-allergic child. This is not yet a routine procedure in pediatric practice although with the simple and effective method described by Tuft (7, 8) and favored by Ratner (6) it could very well be. For children three intradermal injections of 0.05 cc., 0.10 cc., and 0.15 cc., and for adults 0.10 cc., 0.15 cc., and 0.20 cc. of the triple vaccine at one or two-week intervals are recommended. There is little or no reaction. A stimulating booster dose of 0.10 cc. should be given every three years (although it is probably effective even after five years) or just previous to going to camp or to a typhoid area. Typhoid prophylaxis should always be carried out if requested by the camp, if there is any question about the food or the water supply of the camp either for drinking purposes or for swimming, or if the campers are to be taken on long hikes or other excursions where this problem might arise.

The most common allergic condition of the child of the camping age is pollinosis. The parents should take advantage of the opportunity of sending the child away to camp by sending him to a camp in an area as free as possible from the pollen to which he is sensitive. The child's physician should be in a position to advise the parents as to the locale of such camps. Such information can easily be obtained from the bulletin published by the American Academy of Allergy (1). Since ragweed pollinosis is the most common form, it is unfortunate that the conventional end of the summer camping season, because school starts immediately afterwards, is Labor Day. This, in many places, particularly northeastern United States, is the time when the ragweed is at its maximum period of pollination and the child must return to the highly polluted atmosphere of his home city if he is to start school at the same time as other children (4). If possible, arrangements should be made to keep the child in camp until the height of the ragweed pollen season is past at his home. The schooling which the child will miss is more than compensated by the gain in health occasioned by escaping the ragweed pollen.

Even though the child may go to camp in a pollen-free area, he should continue his treatments with pollen while in camp. If he is

symptom free there, he need not be given weekly injections, but may receive injections every two or three weeks, as the allergist may advise. The last dose of pollen in camp should be administered a few days before camp closes and the child, on returning home, should report shortly to his physician with a record of his treatments and experiences in camp from the camp physician. There are several reasons for treating the child with pollen even though he may be going to a pollen-free area. If this is done and something happens, such as an accident or illness, to keep the child at home, he will be protected as far as possible from the pollen at home; the perennial method, which is the method of choice of most allergists, may be continued, and lastly, the continuous treatment with pollen extract, as far as we know, offers the best hope of an ultimate cure other than naturally "outgrowing" the condition.

When the child leaves for camp, rather than send the material for treatment and the directions for its use to the camp physician, it is much more practical to send this by mail to the camp director to turn over to the camp physician. It is the camp director who knows the children and their parents best and who, even more than the camp physician, is interested in the success of the camp, and I have found by experience that the best results are obtained by putting responsibility for the child's treatments directly up to him. If given to the child to take along, the material and directions may be forgotten or kept in too warm a place until arrival in camp. It should be made clear to the camp director that the camp physician should communicate directly with the allergist if there is any doubt concerning the directions or the effect of the injections on the child. With the directions for treatment to the camp physician, or the report to him if the child is not to receive any treatments while in camp, should be listed the child's drug idiosyncrasies, if any, and any other allergens to which the child is clinically sensitive, as well as any special directions which should be followed in camp. It is also important to note the date on which the child's tetanus toxoid immunizations were completed, or the date of the child's last booster dose.

The child should take to camp an adequate supply of all the medications commonly used for the treatment of his allergic condition. These medications should be plainly labeled as to what they

are and how they are to be administered. The child should also take with him to camp his own bedding, special pillows, blankets or blanket covers and mattresses or mattress covers, as are necessary. Unless he rooms by himself, it will also be necessary to lend similar equipment to his campmate.

The problem of swimming is often troublesome. This is permissible in the child with respiratory allergy if it is well under control, but not diving or swimming under water in the case of nasal allergy, unless under perfect control, because of the danger of forcing water into the nose, sinuses or Eustachian tubes where the edematous mucous membranes are easily irritated and infected. If the mere coldness of the water produces an allergic rhinitis or an asthmatic attack, then the child should not swim. Children with chronic atopic dermatitis (dry eczema) may swim, the lesions being protected with vaseline or some other bland protective ointment, if such swimming does not make the skin worse.

The effects of swimming must be judged in each instance by the camp physician and, if not well tolerated, must be discontinued.

Exposure to sunlight is usually well tolerated by eczematous children but occasionally the eczema may be made worse by this exposure or the skin badly inflamed by the sunlight. This is true particularly if the child has had recent treatment with coal tar preparations. If tar preparations are thought desirable for the treatment of the child, then wood tar should be used during the time when the child is exposed to sunlight. Under any circumstances, exposure to sunlight must be controlled so as to prevent its possible ill effects. The customary mad rush to acquire a good coat of tan as soon as possible after arriving at camp must be avoided particularly by eczematous children, in whom the exposure should be gradual, starting with a ten-minute dose and gradually working up to the exposure tolerated by the other children, if possible. It should also be remembered that the skin of eczematous children is also prone to be irritated by overheating and sweating which will likely produce itching crises, so these campers must be observed accordingly.

In general, the allergic child should avoid animals in camp as well as home. If the child is not sensitive to horse dander, he may learn to ride, but all contacts with horses should be out-of-doors, not in barns or indoor riding stables. He should also use one par-

ticular outfit for riding which should be kept separate from his other clothes and not worn at any other time. In crafts and hobbies taught in camp, he should avoid the preparing and mounting of animals with fur or feathers. It would be better to interest the child in mineralogy or geology or the study of fossils or fish. The asthmatic child should not go on overnight hikes where he might have to sleep on the ground or in a barn. He should be taught to recognize and avoid poison ivy and, should he be sensitive to this, prophylactic measures should be instituted before he goes to camp. Abnormally severe reactions to insect bites and stings may occur, and if this happens the nature of the insect should be determined, if possible, so that specific prophylactic therapy may be given if necessary (see Chap. 52).

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ROUTINE PROPHYLAXIS IN ALLERGIC CHILDREN

ONE OF THE most common errors in the treatment of allergic children, particularly those with asthma and eczema, is failure to give routine prophylactic treatment for diphtheria, tetanus and pertussis because of the fear of disagreeable reactions. Since allergic children react to drugs about eight times as often as non-allergic children (see Chap. 45) it would seem reasonable to suppose that an increased incidence of disagreeable reactions to routine prophylactic injections would also occur in allergic children with greater frequency than in the cases of non-allergic children. Studies for the purpose of evaluating this have not yet been made and it is quite likely that if they were, one would find a definitely increased reaction rate in allergic children. However, *from the practical standpoint, this is not important*. In my experience in the general practice of pediatrics dealing largely with allergic infants, I have the impression that untoward reactions of *marked* severity in these infants are not experienced to any significant degree more than in the non-allergic children. Partial confirmation of this impression is indicated by the report of Halpern and Halpern (5) who, over a five year period, collected a series of fifteen children who had convulsions following the injection of the more slowly absorbable multiple diphtheria-pertussis-tetanus antigens. No child who had a convulsion had a history of allergy.

If the parents have been warned against submitting their child to prophylactic injections because of allergy, it is wise for the physician to explain the great importance and little risk attached to such procedures in the allergic child. However, instead of giving the child the full prophylactic dose, a small fraction, say 1/10 or 1/20, of the customary dose should be given and the child's reactions observed. If he has no trouble, as is usually the case, the total amount

remaining may be given in four or five or more divided doses instead of the customary three. The immunological response by this procedure is as good or better than when the injections are given in the orthodox manner.

It is particularly important that the allergic child be immunized against diphtheria and tetanus so that he will never require the corresponding antitoxins as these are commonly prepared from horse serum to which sensitization is easily acquired. If tetanus toxoid has been omitted and tetanus antitoxin is indicated, the bovine preparation* (4) should be used unless the child is allergic to milk or beef. In such instances the physician had best depend upon the so-called "despeciated" tetanus antitoxin,† employing the same precautions as customary for the administration of horse serum since very severe reactions may occur to this also but not with the frequency or to the degree that may occur with the ordinary forms of horse serum antitoxin. Appropriate booster doses of diphtheria and tetanus toxoid should not be forgotten. In the event of severe reactions to diphtheria or tetanus toxoid it should be remembered that even as little as 0.10 cc. of the undiluted toxoid will elicit a satisfactory booster response.

Protection against whooping cough is of paramount importance because of the marked tendency of this disease to aggravate bronchial asthma or initiate bronchial asthma in children with respiratory allergies. While this appears to be quite definitely the situation with such children, it is interesting that in the cases of other children the situation may be different. Byers and Rizzo (1) studied thirty-five children hospitalized between the ages of three weeks and two years because of pertussis and found, after a fourteen-year period, that none had developed asthma or bronchiectasis.

It is important in vaccination against pertussis that a phase I vaccine be used and that it be grown on media prepared with human rather than animal blood to avoid the possibility of sensitizing the child to a foreign protein, or, preferably, as some pertussis vaccines are now made, on a blood free media. Booster doses of pertussis

* Sharp and Dohme.

† Parke, Davis & Co.

vaccine should be administered yearly until the child is five years of age and thereafter whenever exposed. If pertussis does develop it should be treated vigorously with human immune globulin or by the use of hyperimmune human serum.

In recent years the question as to whether or not the child with convulsive disorders should be immunized against pertussis has been considerably debated. This problem was reviewed editorially in the *Journal of Pediatrics* (3) and the consensus among pediatricians appeared to be to the effect that the danger of pertussis to a child with convulsive tendencies was doubtless greater than the danger of developing pertussis encephalopathy following pertussis vaccination. In a case of an allergic child with convulsive tendencies and therefore, so to speak, in double jeopardy following a pertussis vaccine injection, it would be well to give the vaccine starting in small doses as discussed in the second paragraph of this chapter.

The types of vaccine now most commonly used are the so-called triple vaccines which immunize simultaneously against diphtheria, pertussis, and tetanus. In the case of a child with convulsive disorders at least the pertussis vaccine should be given separately as indicated above. If any child given the triple vaccine reacts disagreeably, then the various immunizations should be given separately with due precautions. I have the impression that less severe reactions occur when an alum-treated vaccine is not used. The fact that alum-treated vaccines give a somewhat greater degree of immunity is probably not important if routine booster doses are given. The child should receive a booster dose of the diphtheria-pertussis-tetanus preparation a year after the original injections have been completed and again at five years. A booster dose of pertussis vaccine should be given yearly until the child is five years of age and thereafter if exposed to pertussis. After the first booster dose of diphtheria-pertussis-tetanus, a booster dose of tetanus toxoid should be given every four or five years thereafter unless such a dose is indicated in the meantime because of injury.

It is always in order to call attention to the fact that children with eczema should not be vaccinated against smallpox and children without eczema should not be vaccinated when there are other children with this condition not yet protected by vaccination. The

reasons for this have been detailed elsewhere (see Chap. 20). The presence of other allergic diseases is not a contraindication to smallpox vaccination.

Just when to vaccinate a child who has had atopic dermatitis is a moot question. Chobot (2) stated that vaccination against smallpox is contraindicated in those who have eczema or have had it within a year. My practice is to vaccinate such children during the summer, if their skin clears and remains clear at that time for two or three weeks. The mother should be instructed to make no changes in the diet, environment or other factors in the regime, for at least two weeks after vaccination. I have never seen generalized vaccinia as a result of vaccinating such an infant in my practice.

Whether or not to give routine prophylaxis injections against diphtheria, pertussis, and tetanus during the summer months when poliomyelitis occurs more frequently is, in my opinion, a policy which should be decided both for the protection of the patient and the physician, by the local health authorities. It has no bearing on allergic considerations. Other phases of prophylaxis which might well be considered in a discussion of this nature will be dealt with in Chapter 67.

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THE PROPHYLAXIS OF ALLERGIC DISEASE*

IN 1931, Rowe (34) made the statement that allergy, next to infection, is probably the most important single agent in human symptomatology. While the growth of psychomatics in the years which have since elapsed might well offer a challenge to Rowe's statement, no one can deny the great importance of the allergic diseases and the desirability of developing prophylactic measures against them. Since most allergic disorders begin in childhood, prophylaxis, which is the ideal form of therapy, is the particular province of those dealing with children. We are only now, through studies of the hypothalamus-pituitary-adrenal axis, beginning to get leads in a direction which may ultimately reveal the fundamental constitutional abnormality which renders an individual susceptible to allergic disease. Until this is known, although perhaps not even then, a completely satisfactory or even rational program for the prophylaxis of allergic disease cannot be advanced. Nevertheless, certain facts are known and theories have been brought forward which deserve consideration in the study of this problem.

Although there had been many scattered references to various phases of the possible prophylaxis of allergic disease, the first paper devoted exclusively to this subject was published by Peshkin (26) in 1930, and specifically referred to bronchial asthma. The first publication on the general subject of the prophylaxis of allergic disease was written by Glaser and Landau (15) in 1936, followed in 1938 by a comprehensive discussion by Ratner (29). The subject has since been reviewed by a number of others (25, 22, 37).

It is generally accepted by most investigators, with Ratner (32) a notable exception, that the tendency to suffer from allergic disease

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is inherited. If this is the case, although it is impractical to urge that individuals with allergic disease should not intermarry, it should, nevertheless, be pointed out that such a marriage carries with it certain risks. Naturally, this does not always mean that one or more of the offspring will suffer from severe allergic disease. The offspring may not present any allergic tendencies or may merely demonstrate a transient atopic dermatitis (eczema) or a mild pollinosis. On the other hand, no physician can fail to be impressed by the tragedy of a situation in which one or both of the parents may be disabled by asthma, for example, and all of the children afflicted with severe forms of this or other allergic diseases. The suffering involved, and the economic and psychic strain placed upon the family, may be very real and very serious.

Every human being, and probably every animal, is potentially allergic in that under certain conditions of health and environment, allergic sensitivity may be acquired. However, if we accept the concept that heredity is an important element in the development of allergy, we may then consider that for purposes of prophylaxis a potentially allergic child may be defined as one who has one or more allergic parents or siblings (12). A study (13) in my practice revealed the astonishing fact that approximately 60 per cent of such children developed major allergic disorders before they reached six years of age. This, in itself, argues strongly for a hereditary factor in allergy since even without detailed statistical studies it is obvious that 60 per cent of the average pediatrician's practice, as regards children six years of age or less, does not consist of major allergic disease.

It is not the purpose of this discussion to indicate fully all the pitfalls involved in the study of heredity in allergy. I should only like to point out that certain important allergic diseases of infants and children, such as colic (in those instances where its allergic origin can actually be proved), the recurrent upper respiratory infections secondary to allergic nasal mucous membranes, perennial allergic rhinitis, and migraine in childhood of proved allergic origin may be frequently forgotten when the histories of older children and adults are taken. This is true even if these conditions had been actually diagnosed properly, which in many instances is not the case. This, to a great degree, negates the value of the history in studies of

heredity. It is only when children are carefully observed from birth by a physician trained in allergy, that the true incidence can be determined. Some allergic diseases particularly characteristic of children occur much more frequently than is generally realized. For example, in a study (24) of 516 allergic patients in my practice, ten years of age or less when first seen, recurrent upper respiratory infections on an allergic basis occurred in 30 per cent and perennial allergic rhinitis in 28 per cent. There are certain compensating mechanisms which tend to correct errors in computing the frequency of allergic diseases from the history alone. The two foregoing diseases frequently coexist, and many allergic diseases of infancy and childhood are followed by other allergic diseases as the child grows older. For example, 42 per cent of the children in our series with recurrent upper respiratory infections on an allergic basis and perennial allergic rhinitis, subsequently developed asthma or some other major allergic disease.

Another compensating mechanism is that in the past atopic dermatitis (eczema) and seborrheic dermatitis (which is not an allergic disease) have not been sharply differentiated. However, one would hesitate to say that the present published studies of heredity in allergic disease are probably accurate because the errors of computing their incidence are subject to correction in the right direction because of these compensating factors.

Assuming that one or more of the parents or siblings in a given family are allergic, the next point to consider is whether any form of management of the pregnant mother of a potentially allergic infant may help prevent allergy in the expected child. Shannon (36), as long ago as 1922, in order to prevent or minimize sensitization of the fetus to important foodstuffs, recommended as a general prophylactic measure that all pregnant mothers should be cautioned to eat a large variety of foods and only relatively small quantities of any individual articles of diet and that eggs be restricted rather than forced in the diet of the mother. The observations of Shannon in this respect have since been greatly amplified and extended by Ratner (see Chap. 6). In my opinion it is sound practice to apply these principles, which, though having the possibility of doing much good can do no harm, and I routinely advise the pregnant mothers of potentially allergic infants to avoid eggs as such and foods consisting

largely of egg. It is also recommended, and I am sure this will be regarded as rank heresy, that the mothers drink not more than a pint of milk a day, boiled for ten minutes, and also that they eat no cheese. They are instructed to make meats in variety their chief source of protein and to take added calcium and phosphorus to make up for what they do not get in milk. The same diet is given the mother in those rare instances where she can be persuaded to nurse her baby. The instructions given the mother for this purpose are noted in Table XXIX.

Having now brought our potentially allergic child into the world

TABLE XXIX

RECOMMENDED PROPHYLACTIC MEASURES FOR EXPECTANT MOTHERS
IN ALLERGIC FAMILIES

1. Every effort should be made to breast feed the baby as completely as possible. We know that the completely breast-fed infant has seven times as many chances of escaping eczema as the bottle-fed baby.
2. The mother should eat no eggs during her pregnancy. This does not mean she should be on an egg-free diet, but eggs as such and foods consisting largely of eggs, such as angel cake or custard, should be avoided. Cheese should also be omitted.
3. She should not drink an excessive amount of cow milk. A pint a day should be given, preferably boiled ten minutes, but in addition to this, calcium and phosphorus should be supplied in adequate quantities from other sources, as for example two or three Parke-Davis Nutritive Capsules three times a day, or some equivalent preparation.
4. The mother who is herself allergic should avoid those foods and other allergens which she knows cause her trouble.
5. She should eat a rather wide variety of food and not concentrate as pregnant women occasionally do on just a few articles of diet.
6. The above directions should be followed as long as the baby is nursed. When the mother stops nursing the baby, she may return to the diet she was on before pregnancy.

we must next consider the subsequent steps. Breast feeding is urged since Grulee and Sanford (16) (even without placing the nursing mothers on the modified diet just mentioned), have shown that the breast-fed baby has seven times as many chances of escaping eczema as the bottle-fed baby. If the mother will not or cannot nurse the baby an attempt is made to start the infant on soy bean milk. The basis for this procedure is highly interesting.

When I first started practice in 1929, it was the custom of many pediatricians to start infants on raw egg yolk at the age of three months. This method of feeding had recently been introduced because at that time there was very widespread interest in rickets and anemia in infants and egg yolk was believed to be a good agent for the prophylaxis of both. It was soon discovered, in the course of routine feeding of raw egg yolk to children three months of

age, that many developed rashes or other evidence of intolerance and within a few years this practice was almost universally discontinued. Egg yolk subsequently was not introduced into the diet until the age of six to nine months when it was much better tolerated. *This observation suggested that during the interval between three months of age and six to nine months of age the infant developed some type of protection against allergy to egg.*

It was well known at that time, as a result of precipitin studies (3, 8), that egg white protein could pass unaltered into the blood stream through the intestinal barrier. Reactions to egg yolk, for all practical purposes, are reactions to the egg white contained in the yolk. It was at first thought that perhaps the immunity to egg protein acquired as the child grew older was due to some anatomical change which would no longer permit the passage of unaltered egg white. However, with the development of the passive transfer reaction it was shown (31, 39, 41, 44, 45) that the intestinal tract is permeable to unaltered egg white and other proteins at any age. It thus appears evident that the protection acquired by the infant against egg white as the child grows older is immunologic in nature.

As I became increasingly interested in allergy in infancy, it became increasingly evident that cow's milk was responsible for many disagreeable allergic phenomena, as has been so ably described by Clein (6). In his practice, which is the practice of the pediatric allergist, he estimated its incidence as high as one infant out of every fifteen or approximately 7 per cent. What it is in the practice of most pediatricians not majoring in allergy is not known, but I am sure it is much higher than is generally suspected.* With the knowledge that infants within the relatively short period of three to six months could develop immunologic protection against such a potent allergen as egg white, the thought occurred that if they could be started on some other food than the traditional cow's milk during this period of physiologic immunologic immaturity, the symptoms of milk allergy might be avoided, minimized or even prevented. Consequently the incidence of atopic dermatitis (eczema) and intestinal intolerance to cow's milk, which comprises two of the most exasperating syndromes with which those dealing with infants

See also Chapter 61.

must contend, might be minimized or even prevented. That such a possibility existed was indicated by the work of Grulee and Sanford (16), mentioned above, to the effect that seven times as many infants developed eczema on cow's milk as compared with infants fed breast milk. Breast milk, which is the human infant's only "natural" food, as contrasted with cow's milk which is a "natural" food, not for the human infant but for calves, at least during the first few months of life, would appear to be the ideal food on which to start feeding the newborn infant. However, breast milk is not commonly available and although at times can be purchased, is very expensive and these facts preclude its general use in the feeding of potentially allergic infants. It is also now well known that a variety of substances ingested by the nursing mother may pass into breast milk to cause allergic disturbances in the infant (see chap. 60).

For the above reasons it is desirable to have readily available an adequate substitute for breast milk which should also be of reasonable cost. The milk of other mammals, as the goat, is not commonly satisfactory. (For a discussion of this subject see Chap. 62.)

Hill and Stuart (18), in 1929, as discussed in Chapter 62, introduced a commercially available soybean milk and in the same year Tso (43) reported on one infant raised from birth to the age of six months on a soy bean milk. Shortly after the publication of these reports I began feeding newborn potentially allergic infants soy bean milk as their sole source of protein. Other than breast milk and soy bean milk only meat base milk (10) has been used and this in but a very few cases.

The starting formula for the infants was usually one-third of a commercial soy bean preparation* and two-thirds water which was gradually increased to equal parts soy bean milk and water as the infants became accustomed to the formula. Hill (17), in commenting upon our work, while granting that if well-tolerated soy bean milk will nourish an infant as well as cow's milk, has pointed out that soy bean formulae are likely to cause diarrhea and irritation of the buttocks which, in newborn infants, may become matters of serious

* These experiments were for the most part carried out using the liquid Mull-Soy of the Borden Company. Since the completion of the original study we have been using the new powdered Mull-Soy which is often tolerated by infants with whom the liquid preparation disagrees.

concern. Hill's warning is appropriate and timely. The feeding of the newborn should be undertaken only by those who are well trained in this respect. However, when diarrhea and or sore buttocks appeared, we endeavored to treat this in the usual manner, but if we were unsuccessful we discontinued the soybean preparation. This was, however, necessary in less than 15 per cent of our cases, and this includes those infants where intractable colic and emesis also appeared to be due to the soybean feeding.

The results of this method of feeding, as far as the prophylaxis of allergic disease is concerned, far exceeded our expectations. It is *a priori* reasoning that if one does not feed cow's milk to an infant, allergy to cow's milk does not occur. Only 8 per cent of our experimental group developed eczema as compared with about 30 per cent of the control group. The eczema in this 8 per cent of the cases, of course, was due to other factors than cow's milk. In a few instances where there was a congenital sensitivity to cow's milk, the infants reacted when again fed cow's milk at an average age of six months. In only one instance, however, was the milk sensitivity retained after further prolonged abstinence from cow's milk.

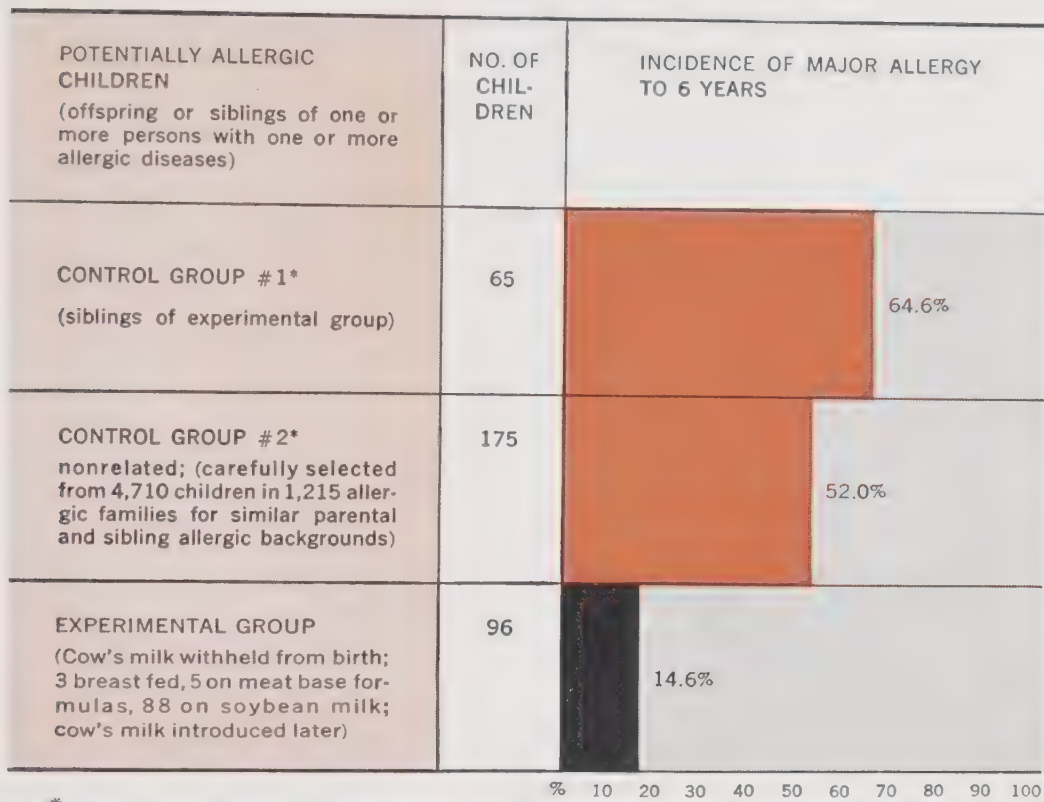
Hill (17), again commenting upon our work, inferred that while withholding cow's milk from the diet the first few months of life, would logically minimize or prevent the development of allergy to cow's milk, that this could not reasonably be expected to prevent subsequent sensitization to other allergens as the child grew older and his view certainly appears to be good common sense. However, previous studies (24) in my clinic on the incidence and progression of allergic disease in pediatric practice, had apparently confirmed the observation, previously made by many others, that once the allergic state is established it tends to be followed by the development of other allergic diseases. For this reason, we thought it would be interesting to see what happened to our patients as they grew older. Much to our surprise, we found that only about 15 per cent of our experimental group developed major allergic diseases before the age of ten years as compared with about 60 per cent of our control group. This finding was so astonishing that we felt our experimental group might well be weighted in the direction of a greater incidence of allergies than might occur by chance in a random sampling of potentially allergic children. The reason for this was, of course, that these infants were placed on the experimental regime because their

siblings or others in the family had suffered from various allergic diseases. Consequently, a second control group was selected. From reviewing the histories of 4,710 children in 1,215 allergic families, 175 were selected to comprise the second control group of this study. These children were followed for the same number of years as their opposite members in the experimental group and had the same number of younger siblings with closely similar allergic histories. Their parents, also, had allergic histories closely resembling the histories of the parents of the children of the experimental group. Members of the sibling, as well as the non-related control group, were considered as having allergic disease only if their symptoms occurred by or before the present age of their counterparts in the experimental group. We feel it is highly significant that in this non-related control group 52 per cent of the children developed major allergic disease as compared with 64 per cent of the sibling control group, a truly remarkable close correlation. Thus there is approximately a fourfold incidence of allergy in potentially allergic children started on cow's milk from birth as compared with those started on soy bean milk. This study is graphically summarized in Figure 42.

It must be emphasized that to be successful, this regime must be instituted from the moment of birth. To give a potentially allergic newborn infant a trial feeding of cow's milk ignores the basic premise of this procedure, namely that these children have an immunological immaturity in the first few months of life which makes them predisposed to become sensitized to the first foods which are introduced into the diet.

If the above method of prophylaxis actually reduces the incidence of allergic disease to the degree indicated, and it is my considered opinion that it does, the possibilities this procedure offers for improving the health of our nation (not to mention others) are fantastic. Swartz (42)* who reviewed the literature of this subject in

* The original references are not mentioned in this publication. However, when questioned as to their source in a personal communication Swartz replied as follows: "The *World Almanac* published by the *World Telegram and Sun*, 1952, page 398, presents tables of United States population from which is derived the figure of approximately 40 million for the age group fourteen or under. Vaughan and Black, *Practice of Allergy*, 2nd Ed. (St. Louis, Mosby), Chapter IX established a 10 per cent plus major allergy and a preponderance of the onset of allergy in the first and second decades." Swartz also checked all the original source material for this chapter.



* Observed for same lengths of time as counterparts in experimental group. Table adapted from: Glaser, J., and Johnstone, D. E.: Prophylaxis of Allergic Disease in the Newborn, *J. A. M. A.* 153:620, Oct. 17, 1953.

FIG. 42. Incidence of the development of major allergic disease in potentially allergic infants fed from birth for varying periods of time on a substitute for cow's milk as compared with the incidence in two independent control series.

detail, states that one out of every eight children in the United States is an allergic child, and at least 10 per cent of the total population suffers from allergic disease. Certainly this study opens up a vast new field for the pediatrician in the area in which he is most interested, that of prophylaxis.

It is not to be expected that such a completely new and revolutionary point of view would be accepted without criticism. However, in the interval which has elapsed since this work was first presented at the meeting of the American Academy of Allergy in Boston only scant discussions of this have appeared in the literature. The most important of these were those of Hill (17) which have been previously discussed. Other minor criticisms are reviewed elsewhere (14).

The impression should not be obtained from the foregoing that cow's milk is to be regarded as food which is highly dangerous to the human race. Nothing could be further from the truth. For the individual with whom cow's milk agrees, and fortunately this includes the vast majority of the human race, *it is without doubt the greatest gift of food that nature has given to mankind*. However, in the case of potentially allergic children, the physician is confronted with a very important aberration of nature. It is to be hoped that by following the principles of feeding the potentially allergic newborn infant just elucidated, that in the future many who would otherwise suffer because of the too early feeding of cow's milk, will be spared this and thus eventually be enabled to enjoy this most valuable food throughout the rest of their lives without impairment to their well-being.

Based on the same general reasoning for starting potentially allergic infants on soy bean milk instead of cow's milk to avoid sensitizing the infants to cow's milk, I feel it unwise to start these infants on such an important food as wheat for the first cereal. The infant should be started on other cereals, as barley, oats, rice, and corn, using these successively so as to give the infant as great a variety as possible, introducing wheat when the infant is between nine and twelve months of age. Buckwheat (which is not a true cereal) should not be used because of its high sensitization potential. Mixed cereals offer no particular advantages for potentially allergic infants but may be used after the component cereals have been introduced into the diet. Sensitivity to fruits, vegetables and meats occurs much less readily but the same general principles apply. One should use as much variety as is practical. The potentially allergic infant should not be fed orange juice daily, despite its low antigenicity when free from seed and oil (30), but a variety of biogenetically unrelated juices, the ascorbic acid deficiency of some of these being made up, when necessary, by the addition of ascorbic acid. Fish should not be added until the infant is at least a year of age, and nuts not until much later. In this connection, because peanut butter is a favorite food for young children, it should be pointed out that the peanut is not a nut but a legume. Egg, when eventually added to the diet, preferably not before the age of one year, should be started gradually in the form of hard-boiled egg yolk, hard-boiled egg white being added

if the yolk is well tolerated, and later, if this agrees, egg cooked by other methods may be tried.* Allergy to the vitamins most important in infancy is so rare that it need not be considered as far as the potentially allergic child is concerned, provided simple A, C and D preparations are used.

A problem of much interest in pediatric practice at the present time is whether or not the early introduction of various foods into the infant's diet is beneficial or harmful. Information regarding this seems to be based on opinion, as indicated by the report of Butler and Wolman (5) rather than on facts established by the kind of long-term study necessary to solve such a difficult problem. Deisher and Goers (7) have made a very fine beginning in this direction. They divided a series of eighty-five new born infants into two groups, in one of which solids were introduced during the first four weeks and in the second during the ninth to the twelfth week. At the end of a year no significant differences could be observed between the two series of infants.

It is certain that even the newborn infant can adapt to a variety of foods and thrive very nicely from birth as the successful feeding of these infants with soy bean milk and meat base milks previously discussed so amply indicates. The most highly allergenic foods commonly used in early infancy are cow's milk and egg, and if egg is avoided and cow's milk replaced by a food of equal value but of low antigenicity (as soy bean milk) and others used in variety, it is unlikely that any harm from the standpoint of allergy will result. It is also desirable that wheat, which will be the principal carbohydrate food as the child grows older, should be avoided, and the other cereals used instead, particularly since it has been demonstrated that allergy due to cereal grains, especially wheat, is responsible for some cases of the celiac syndrome as has been discussed in Chapter 11. While it might appear that nature has given the answer as to the proper time to introduce such polysaccharides because of the fact that pancreatic amylase cannot be demonstrated until the infant is three months of age (2), this is not the complete answer because the starch splitting enzyme, ptyalin, is present in the saliva of the fetus during the last half of gestation and disaccharide splitting enzymes are present in the intestinal juice for sometime before birth (38).

* See also Chapter 63.

All factors considered, it would appear that the evidence favors that group of pediatricians who feel that the early introduction of almost anything edible into the diet of the very young infant is due to social pressure rather than to good medical judgment.

It was pointed out by Hutinel (19), as long ago as 1908, and later by Schloss (35), that following acute gastrointestinal episodes, probably due to the increased permeability of the bowel, infants and children may become sensitized to foods which they previously tolerated. In acute gastrointestinal disturbances and in their convalescence, therefore, a variety of cooked foods of low antigenicity should be used, especially in children with allergic tendencies.

There are also occasional instances reported of sensitization apparently acquired by over-indulgence in specific foods. Stuart and Farnham (40) mentioned the case of a man who as a child drank a can of glue on a bet, and thereafter reacted on eating fish with severe allergic manifestations. Alvarez and Hinshaw (1) reported one man who in his student days ate at one sitting two pounds of dates left over from a fraternity party and thereby became highly sensitized to this food. Another became sensitized to milk by taking from four to six quarts a day during treatment for tuberculosis. After that small amounts produced nausea and diarrhea. Ratner and associates (33) have warned that fad diets, which are usually composed of a limited number of foods, and very often raw foods, may be a potential source of food sensitization. In this connection, it is interesting that allergy to horse serum may be acquired by the eating of horse meat (4).

The environment of the potentially allergic child deserves careful consideration. The bedroom should be designed so as to be as free from house dust as possible, and also free from cooking odors, tobacco smoke, cleaning fluid, moth balls, gasoline (as in a room over a garage), and other strong or irritating odors. An unusual instance illustrating the importance of environment in the acquisition of hypersensitiveness, is mentioned by Ratner (30) who reported the case of an infant whose bedroom window faced a stable and, apparently as a result of this, the infant acquired sensitivity to horse dander, with a crossed reaction to horse serum.

The furniture of the room is also important. Most of the better quality of crib mattresses are satisfactory since they have plastic

dust-proof covers. As the child grows older and needs a larger mattress, sponge rubber is the ideal material for this as well as for the pillow. Both should be enclosed in dust proof casings. The bedding should be free from silk, wool, hair, feathers and kapok. Good blankets made from synthetic fibers are now available. Fortunately, most of the better animal toys have imitation fur made of rayon plush, which is harmless, and are stuffed with a good grade of cotton relatively free from the seed, which is a very powerful allergen. There should be no fur- or feather-bearing pets, regardless of negative skin tests or the apparent harmlessness of these pets on clinical observation. Insecticides should be free from allergens, especially pyrethrum, which is closely related antigenically to ragweed.

The routine prophylaxis of diphtheria, pertussis, and smallpox tetanus in allergic children has been discussed in Chapter 66 and need not further be considered here.

Potentially allergic or allergic children exposed to measles should be treated with immune globulin for the purpose of modifying the disease because of the tendency of pulmonary complications in such children to pave the way for asthma. Even mild measles should be vigorously treated with antibacterial drugs so as to reduce the incidence of pulmonary complications which, in a child with respiratory allergic disease, has a marked tendency to hasten the onset of asthma. Karelitz and associates (20) have shown the marked efficacy of penicillin in preventing the complications of measles.

The incidence of penicillin reactions and the greater frequency of their occurrence in the allergic child has been previously discussed (see Chap. 45). It appears to be a matter of common observation that the oral route sensitizes much less frequently than the parenteral and that the more penicillin a given person receives, the more likely he is to become sensitized. It is, therefore, in the interests of good practice not to use the parenteral route when the oral route will suffice, and, also, not to use penicillin when other antibiotic substances or sulfonamide drug will accomplish the same purpose. It was the consensus of allergists in replying to a questionnaire on this subject (23) that no one antibiotic should be used constantly but that the physician should have some system of rotating the various antibiotics for successive illnesses, thus diminishing the chances of sensitivity to any one antibiotic drug.

It is also important that the allergic child be protected from other members of the family who have acute or chronic respiratory infections (21, 27). In this connection it should be mentioned that it is highly essential that the allergic child be adequately protected from the weather. The current fashions in children of bare heads and bare legs in all kinds of weather is not to be condoned in allergic children.

The inadvisability of removing the tonsils and adenoids or doing intranasal operations on children with pollinosis during the pollen season has previously been commented upon (Chap. 31). Such operations predispose the child to asthma.

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ADDENDA

The following tables are for the purpose of supplying specific directions to patients in addition to those already previously included in the text. Which should be used are decided upon as a result of the complete study of the patient as discussed in Chapter 5. Where a table discusses more than one allergen, those applicable to the particular patient are checked in red. Any suggestions for changes or the addition of further instructional sheets will be much appreciated by the author and publisher in case a subsequent edition of this book is published. If this is done it may be possible to more or less standardize and improve an important function of the physician, i.e., the giving of specific, complete instructions to the patient in as simple language as possible. Any physician is free to copy these instructions for distribution to his patients.

TABLE XXX

ENVIRONMENTAL CONTROL*

We know that eczema can be caused by foods, by substances inhaled from the air (inhalants) and by substances which come into direct contact with the skin (contactants). The object of environmental control is to reduce the chances of difficulty from inhalants and contactants.

1. The bedroom should be as free from dust as possible—see special direction sheet.

2. Avoid contact with feathers, fur, animal hairs, wool and silk. These should be eliminated as far as possible in room furnishings and toys and when not eliminated used according to the suggestions below.

3. There should be no uncovered feather pillows in the bedroom. If you are unable to obtain a sponge rubber pillow, the next best thing is to cover your present pillow with a dust proof cover. This cover must be absolutely dust proof and have no breather holes.

4. No fabric other than previously washed white cotton fabric should come into contact with the skin. The cotton clothing should not be washed with other clothing and great care should be taken to thoroughly wash all the soap out of the clothing.

5. All wool blankets should be enclosed in durable cotton blanket covers which are frequently changed and washed. If this is not possible, pin the blankets between cotton sheets which are frequently changed and washed.

6. Wool clothing should be lined with thick cotton cloth. Especial precautions must be taken around the wrists, ankles and neck. Great care should be used to avoid wetting such mixed clothing, especially in the places just mentioned.

7. In picking the child up, do not allow his skin to come into contact with wool or silk clothing or furs which you may be wearing.

8. Use no soap on the body or face or scalp. Use only the items indicated below, the directions for the use of which are on the container or supplied herewith on a special direction sheet.

9. Because of your intimate contact with the child, you are able to make observations impossible for your physician. If you get any ideas as to the possible cause of the difficulty, write them down so that they will not be forgotten and bring them to your physician's attention at the next visit. Study all directions carefully. If there is anything about them you don't understand, telephone or write this office. Remember that what we are doing now is not only for the purpose of relieving the patient's present difficulty but is also for the purpose of trying to prevent other and often worse trouble in the future.

* These instructions are commonly given to the parents of children with atopic dermatitis.

TABLE XXXI

THE DUST-FREE BEDROOM

All surroundings of the dust sensitive patient should be as free as possible from dusts of all kinds. Most people cannot control the dust conditions under which they work or spend their daylight hours, but everyone can to a large extent eliminate dust from the bedroom. While the directions below may seem difficult at first, experience plus habit will make them simple, and the results will be well worth the effort.

1. Steam or hot water heat is preferable to hot air. If there is a hot air furnace outlet in the room, a dust filter made of several layers of cheesecloth or some other adequate material must be installed and this filter changed frequently. Holes or cracks in the floor around heating or other pipes must be sealed, and for this purpose adhesive tape is useful, although for some cracks scotch tape is adequate. Other suitable filters for this purpose may be obtained at most hardware stores.

2. The room must be completely emptied, just as though you were moving. Empty and clean all closets and if at all possible store contents elsewhere and seal closets. Give the woodwork and floors a thorough cleaning and scrubbing to remove all traces of dust. Every inch of exposed or hidden surface must be made spic and span. Floor or linoleum should be oiled or waxed. Linoleum, if used, should be cemented to the floor. (If flax sensitive, linoleum should not be used; use wooden floor covered with paint containing no linseed oil.)

3. The room should contain only one bed, preferably a simple iron bed. If a second bed must be in the room, it must also be prepared in the same manner. Outside the room the bed and springs should be scrubbed. If box springs are used, they must be covered with dust-proof casings. The mattress should be enclosed in a dust-proof cover.

4. Do not use any kind of mattress pad. Do not use fuzzy wool blankets or feather or wool stuffed comforters. Use only washable material on the bed. Sheets and blankets should be laundered frequently.

5. A wooden or metal chair which has been scrubbed may be used in this room. Rag rugs washed once a week may be used on the floors. Plain, light curtains washed once a week may be used on the windows. The room should contain a minimum amount of furniture and furnishings and no upholstered furniture.

6. The room must be cleaned daily, and given a thorough and complete cleaning once a week. Clean the floor, furniture, tops of doors, window frames, sills, etc., with a damp cloth or oil mop. Air the room thoroughly. Then close the door and windows until the patient is ready to occupy the room.

7. Keep the doors and windows of this room closed as much as possible, especially when you are not using the room. Use this room for sleeping only. Dress and undress and keep clothing in another room.

8. If the patient is a child, do not keep toys which will accumulate dust in the room. Do not use stuffed toys. Use only washable toys of wood, rubber or iron.

9. All animals with fur or feathers must be kept out of the room.

10. Care must be taken to keep down the dust throughout the entire house. Go over all floors and furniture with a vacuum cleaner at frequent intervals—once a day if possible. Following this the house should be aired thoroughly. Cleaning must be done while the patient is away from the house. Use a damp or oiled cloth to avoid raising dust. If the patient has to do the cleaning, a dust mask must be worn. A simple inexpensive mask may be obtained at this office.

11. Patient should not go into any room while it is being cleaned. Be careful not to handle objects that are covered with dust, such as books, boxes, or clothing that has been stored on shelves or in cupboards over a long period of time. Stay away from attics and closets. If any of the above must be done by the patient, a dust mask should be worn.

12. If an insect spray is necessary, use Kilit or Cederene. D.D.T. may be used if not mixed with pyrethrum.

13. Avoid odoriferous substances as perfumes, camphor, moth balls, tar, wet paint, gasoline, etc.

TABLE XXXII

MISCELLANEOUS INSTRUCTIONS

By the word "epidermoid" is meant the dust or dander from the fur or feathers of an animal. Allergic individuals possess the property of becoming sensitized with relative ease to these substances which should be avoided as a prophylactic measure, regardless of the results of skin tests. **THERE SHOULD BE NO ANIMAL PETS WITH FUR OR FEATHERS IN THE HOUSEHOLD OF AN ALLERGIC INDIVIDUAL.**

Patients sensitive to epidermoids should avoid places where animals are congregated as zoos, circuses, barns, and horse, dog and other pet shows.

The precautions most important to be taken in your individual case are indicated by the check marks.

Animal Pets: If you have no such pets, do not acquire them. If you have and they do not appear to bother you, do not replace them if they die. In some cases of mild sensitivity the pet may be kept outside the house but the safest measure for the patient is to have no pets of this character. If, in your special instructions, you are advised to avoid any particular animal, then this animal should be removed from your home and exposure to it carefully avoided.

Feathers: The most common source of feathers in the home is the pillow. The best pillow for an allergic individual is made of sponge rubber or certain plastics like Acrilan or Dynel (vinyl). They cost about the same as good feather pillows and like such pillows will last a lifetime if given proper care. Such pillows are best enclosed in dust-proof covers to prevent dust from settling into the stuffing. They may be obtained from drug stores or department stores. There should be no feather or down pillows or comforters or feather beds in your bedroom and preferably not in your house. Avoid everything stuffed with feathers. Avoid cleaning the feathers from fowl and entering chicken coops.

Mattress: The best mattress for an allergic individual is made of sponge rubber enclosed in a dust-proof cover. Mattresses stuffed with non-allergic plastics should soon be available. The next best is an innerspring mattress enclosed in a dust-proof cover.

Wool: Coarse woollens are to be avoided. Woolen blankets should be enclosed in good dust-proof covers or pinned securely between thick cotton sheets which are frequently changed and washed. Cotton covered blankets containing glass wool, which is lighter and warmer than sheep wool, are now available. Do not have wool rugs in the bedroom. Blankets made with synthetic plastic fibers are also now available.

Coarse sweaters and coarse wool socks and stockings are also to be avoided. Wool fur in the form of sheepskin linings for coats and coat collars and gloves should be avoided. Winter wear such as coats and snow suits made of cotton is now available. Celanese and nylon and other synthetic fibers are also available.

Ordinary finely woven wool cloth does not cause trouble except in cases of extreme sensitivity.

Cottonseed: Most inhalant allergy due to cotton is due to particles of cottonseed. This is found particularly in the stuffing of pillows, sofa cushions, mattresses, bed pads, blankets, and furniture. Where such articles cannot be eliminated, they should be covered with dust-proof covers. Most midget golf courses are covered with ground cottonseed mixed with other substances. Cottonseed is also found in some cattle and poultry feeds.

Kapok: (Also called "silk floss")—is a plant product related to cotton. It is most often found in pillows, especially sofa cushions, and mattresses. It is also used in the stuffing of life preservers and some mattresses. All kapok crumbles to dust in the course of a couple of years and is best avoided by the allergic individual.

TABLE XXXIII
MISCELLANEOUS INSTRUCTIONS

Horse Hair

Sensitive persons must avoid not only horses and stables but also persons and objects directly or indirectly connected with the handling of horses. For example, contact with clothing worn for horseback riding may cause as much trouble as direct contact with horses. If you are sensitive to horse dander, members of your family who ride should change their clothes and wash themselves carefully before they return home.

Uses of horse hair: In mattresses; the long hairs may be woven into coarse cloth used for covering sofas, cushions, chairs and seats of railroad cars; under the name of "crinoline" for lining and padding clothes; lining shoes; making gloves, sieve bottoms, press cloths, sacks and bags.

Mane and tail hair of medium length is made into clothes-, hair-, shoe- and tooth-brushes, this hair makes excellent stuffing material for automobile seats, cushions, furniture, mattresses and pillows. Hog, cow and horse hair are often mixed together for this purpose.

Fishing lines, ropes, soldier's hat plumes and wigs may be made of horse hair.

The body hairs are used in the manufacture of felt hats and in textile industries. Colt and pony skins are of value as furs.

Short hair removed from the skins at tanneries is employed as a binder in plaster.

Cow Hair

PADS for placing under rugs or carpets, as Ozite and similar pads with a waffle iron pattern are commonly made of cattle hair and hog hair.

CHENILLE CARPET is made of cow hair.

CHINESE and INDIAN RUGS often contain cow hair mixed with wool and other hairs.

Stuffing material for sofas and chair cushions often contains cow hair; hair from cows' tails is mixed with horses' hair for stuffing mattresses and furniture.

Railway and steamer rugs, horse blankets and other coarse blankets often contain cow hair. Plushes of cheap quality suitable for curtains, upholstery, mantel borders and fur toy animals are often made of cow hair.

Felt for roofing, for covering boilers and pipes of steam engines and for insulating purposes.

Cow hair may be mixed with mortar and plaster for building purposes.

Rope.

Fine hairs from the inside of cows' ears are made into artists' brushes as a substitute for camel hair. Cheap imitation seal skins may be made of cow hair. Calf skin may also be used for imitation furs.

Hog Hair

PADS for placing under rugs and carpets, as Ozite and similar pads with a waffle iron pattern are commonly made of hog and cattle hair.

Hog hair is principally used in the manufacture of brushes; for stuffing upholstered furniture, mattresses and automobile cushions; insulation purposes and mixing with mortar or plaster.

Silk

Although silk is not truly an epidermoid, yet so many allergic individuals who react to epidermoids react also to silk that it has been found convenient to comment upon silk here. This refers to genuine silk made by the silk worm and not to synthetic substitutes such as rayon, nylon, etc. which are usually harmless. If one reacts to silk, then silk should be carefully avoided in clothing and room furnishings. One's clothes, also, should not be washed in water used to wash genuine silk.

TABLE XXXIV

GOAT HAIR

Mohair is the name given to the fine, wooly hair of the angora goat. It is used in the manufacture of Utrecht velvet or furniture plushes widely used in France, Germany, and the United States for upholstered furniture, automobile cushions, and the seats of railway cars.

Portieres, cushions, couch covers, table covers, and curtain materials are made of mohair. Used alone or mixed with wool or silk, it is made into such a variety of articles as the following: dress goods; light weight materials for men's summer suits; or for linings; heavy twill cloth for men's clothes; braid; buttons; bindings; and material for automobile tops.

Fine goat's wool is used in weaving costly Oriental rugs. Mixed with silk it is also found in fine tapestries.

Goat hair is often used as an adulterant of wool used for weaving fabrics.

Imitation "astrakhan" is made from goat hair.

Goat's hair is frequently employed as a stuffing for pillows, cushions, and mattresses. It is also used by manufacturers of felt for hats and insulation purposes.

The hair of angora goats may be used for making doll's hair as well as theatrical and judges' wigs. Very often this hair is mixed with human hair for making wigs and braids for women.

Angora skins with hair attached may be made into rugs and carriage robes.

It is also used for making some artificial furs.

Some fine fabrics called camel's hair are often made of the best mohair and not from the wool of the camel.

The costly Cashmere, Indian, and paisley shawls of the Orient are made of fine wool or down which grows as an undercoat below the long fine hair of some goats.

Commercial fabrics sold as "Cashmere" are various types of ordinary sheep wool.

Goat hair is also utilized in the manufacture of carpets, rugs, ropes, and coarse water-proof fabrics.

Brushes of superior quality are sometimes made of goat hair.

The hair of the common goat may be used in the manufacture of some very coarse fabrics, and ropes.

The refuse goat hair from tanneries is made into coarse yarns, carpets, cheap blankets, and mops. The poorest quality goes into plaster.

TABLE XXXV

RABBIT HAIR PRECAUTIONS

Actual contact with live or dead rabbits must be avoided.

Rabbit fur is used for fur coats, trimmings, carriage robes, linings for gloves, slippers and foot muffs, mattress stuffing, pillows, and quilts.

Rabbit fur may be sold under the name of coney or lapin.

Toy animals may be made of rabbit skin.

Actors may use a rabbit's foot for applying make up; some people carry a rabbit's foot as a good luck charm.

A material resembling kasha contains rabbit hair; rabbit hair is used along with other hairs and fibers in some of the modern fabrics.

Fur of the angora rabbit is said to be ten times warmer than sheep's wool; the soft yarn spun from angora rabbit fur is used for making all kinds of infant's wear, handknitted trimming, crochet work, millinery trimmings, underwear, gloves, hosiery and knee pads for invalids, and rheumatic patients. Alone or mixed with silk it is used in sportswear as sweaters, scarves and hose; also as underwear.

Felt of good quality, particularly for felt hats, is made from rabbit hair. Such felt is also used on sounding hammers of pianos; as insulation against heat in refrigerators and against sound in buildings; in shoes; as washers for cartridges; and as polishing pads.

The fur of the Chinchilla rabbit is more valuable than the other kinds of rabbit fur because in its natural state it closely resembles the fur of the genuine chinchilla. It is sold under such trade names as Chapchilla, Chinchillette, or French Chinchilla.

Rabbit hair may be treated and dyed to resemble the following:—

<i>Fur Imitated</i>	<i>Trade Name</i>
Beaver	Belgian Beaver, Beaverette, Castorette, Electric French, Mendoza, or Meskin Beaver.
Fox	Baltic, Black, Brown, Red or White Fox.
Leopard	Baltic, Coney, French or Russian Leopard
Mink	Minkony and Vionette
Mole	Coney or Electric Mole, Meskin Moline and Moline
Nutria	Nutriette
Sable	French Sable or Sable Hare
Squirrel	Squirrelette, Squirreline
Seal	Australian, Artic, Baltic, Bay, Coast, Electric, French, Meskin, Near Northern, Polar, Red River or Roman Seal; Musratine, Sealette, Sealine

TABLE XXXVI

Flaxseed

The Latin word "linum," from which our word, "linen," is derived means "flax." FLAXSEED is the seed of the flax plant. Skin reactions to flaxseed are fairly common, and this substance should be avoided by individuals who know they have trouble from this substance or who give positive skin tests. Flaxseed may cause reactions when taken as a food (ingestant) or inhaled as a dust (inhalant) or by direct contact with the skin (contactant). An individual sensitive to flaxseed should avoid it in every form.

Ingestants

Cereals: Roman meal & Uncle Sam's Breakfast Food

Flaxseed Tea

Flaxolyn: a laxative

Milk of cows fed flaxseed will cause reactions in very sensitive persons.

Flaxseed extracts are used occasionally in cough remedies.

Inhalants and Contactants

Flaxseed meal as a food for cattle and poultry.

Flaxseed is used in poultry tonics.

Wave sets, shampoos and hair tonics (Kremel) may contain flaxseed.

Bird Lime Carron Oil Flaxseed Poultices Furniture Polish

Linseed Oil Paints and Varnishes Linoleum (Latin, meaning "flax oil"). The dust from old linoleum may cause symptoms. Printers and lithographic ink Soft Soap Some depilatories.

Cloth Materials

These rarely cause trouble except when very coarse or in cases of extreme sensitivity.

Art linen Damask Sheeting Bird's eye (linen) Dress linen Table linen Cambric

Handkerchief Linen Toweling Huckaback Collars and cuffs Oil cloth Sewing thread

Miscellaneous

Insulating material Flaxlinum, used in refrigerators Bi-flax, a base used for insulating plaster Rugs-Klear flax Straw mats Paper Wax Paper (High grade) As a stuffing material for furniture, chair mats and seats, cushions, etc. Fiber Board

TABLE XXXVII
INDIAN GUM (KARAYA GUM)

Indian or Karaya Gum may cause allergic manifestations if inhaled in the form of dust, or ingested as a food or medicine, or on direct contact with the skin. If one is sensitive to this substance it is best avoided in all forms. Besides Indian Gum or Karaya Gum, the common names, a variety of other names is also given to this same substance as: Bassora gum, ghatti gum, gulu, Kadaya gum, Karaia, Katira, Katila, Kuteera, Kawali, koln, loli, pandruk, penari, Sterculia gum, and Velleypentali.

If in doubt as to whether or not a preparation contains Indian Gum it is better not to use the preparation or to find out by writing the manufacturer. The principal sources of exposure or contact to this substance are as follows:—

Denture Adhesive Powders:—Dr. Wernet's Powder	Denture Powder
Dent-a-firm	Stix

Laxatives: Many emulsified mineral oils and other laxatives, also:—

Bassaron (Merrell)	Karabim (Geo. A. Brown & Co.)
Imbicoll (Upjohn)	Mucara (Wyeth)
Kaba (Battle Creek Sanitarium)	Saraka (Schering)

Tooth Pastes: Listeren; Lactona.

Wave Sets: Probably one of the most common sources.

In addition Indian Gum is found in:

- Commercially prepared ices and flavor emulsions.
- Certain brands of gelatin and junket.
- Diabetic foods, including some soy bean and almond wafers.
- Fillers for lemon, custard and other factory made pies.
- Fillers for ice creams and prepared ice cream powders.
- Gum drops and candies with soft centers, as jelly beans.
- Hand lotions of many types.
- Kara jel.

The manufacturers of the following products state that their preparations do not contain Indian gum except as noted:

- Harold H. Clapp, Inc. Baby Foods.
- Jell-O, Jell-O Puddings and D-Zerta, except Jell-P Ice Cream Powder.
- "Junket Preparations" except the Junket Brand Freezing Mix for making ice cream.
- Knox Gelatin.
- Kremel Desserts.
- Royal Puddings and Royal Gelatin Desserts (Standard Brands)

Some cheeses of the Kraft type contain India Gum.

TABLE XXXVIII

PYRETHRUM

This is a common constituent of insect powders and sprays. It is the dried, powdered flower of the pyrethrum plant, a member of the chrysanthemum family. Most pyrethrum used in this country comes from Japan or California.

The most common use of pyrethrum is in the non-poisonous insecticides of which Flit and Black Flag are typical examples. It is also very popular for moth-proofing carpets, draperies and upholstery and to prevent the growth of various other insects in these materials. It is used in insect powders and sprays for the house, garden, and pet animals.

Pyrethrum is occasionally found in medicines, as ointments, particularly for parasites on the human skin and that of animals. Occasionally it is used in medicines administered internally, particularly for intestinal parasites (worms).

Avoidance of pyrethrum at home is usually easy. Away from home, as in the houses of others, theaters and other public places, avoidance may be difficult. The upholsteries and draperies of moving picture theaters where moths are apt to congregate because of the darkness are often impregnated with pyrethrum. It is highly advisable for the pyrethrum sensitive patient not to go into rooms or closets which have been recently treated with insecticide, or wear clothes which have been recently moth-proofed.

Pyrethrum allergy may be seasonal due to the fact that the materials are used seasonally. If avoidance is not possible, hyposensitization may be required.

Cederene Insect Spray and Kay-O Insect Powder are free from pyrethrum. D.D.T. may be used if not mixed with pyrethrum.

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INDEX

A

- ABC potassium mixture, 269
- ACTH (*See also* specific diseases)
 - general considerations, 266
 - in pregnancy, 279
- Adenoids
 - recurrent in nasopharynx, 229
 - in recurrent upper respiratory disorders, 300
 - in relationship to asthma, 228
- Adrenalin, *See* Epinephrine
- Aerosol
 - aminophylline, 243
 - epinephrine, 244
 - penicillin, 235
- Air in extrapulmonary spaces, 223
- Allergic child
 - camp and the, 483
 - characteristics, general, 11
 - facies, 304, 305, 307
 - food dislikes, 12
 - growth and development, 11
 - intelligence, 12
 - intercurrent infections, 14
 - thyroid, 15, 308
 - twins, identical, 16
- Allergic cough, 218
- Allergic dermatoses (*See also* specific diseases), 90
- Allergic disease (*See* specific disease)
 - pathological physiology, 48
 - sequence of body system involvement, 48
 - treatment with steroids, 266
- Allergic facies, 305, 307
- "Allergic salute," 305
- Allergic study
 - summation of, 44
 - instructions for patients, 44
- Allergic syndromes
 - dermal respiratory, 94, 425
 - incidence of, 3
 - progression of, 3
- Allergy clinics, early pediatric. x
- Almond base milk, 459
- Altitude and allergic manifestations, 479
- American Academy of Pediatrics, Section on Allergy, xi
 - Subspecialty Board of Pediatric Allergy, xi
- American Foundation for Allergic Diseases, 265
- Aminophylline, 250
 - suppositories, 243
- Ammoniacal dermatitis, 86, 161
- Anaphylactoid purpura (*See also* Schönlein-Henoch syndrome), 342
- Anesthetics, local, 340
- Angioedema, 311
- Antihistamines, 335
 - dosage, 335
 - toxic reactions to, 336
 - intoxication, treatment of, 337
- Aphthous stomatitis, 402
- Arthritis, allergic, 398
- Asses' milk, 458
- Asthma, bronchial
 - definition, 175
 - intrinsic, 175
- complications, 221
 - air in extrapulmonary spaces, 223
 - atelectasis, 221
 - death, 226
 - emphysema, 221
 - heart disease, 224
 - massive collapse of lungs, 221
 - mediastinal emphysema, 223
 - pneumothorax, 223
 - ribs, spontaneous fracture of, 225
 - subcutaneous emphysema, 223
 - tuberculosis, 225
- differential diagnosis, 183
 - Ayerza's disease, 216
 - bronchiolitis, 202
 - bronchitis, asthmatic, 188
 - bronchotetany, 217
 - capillary bronchitis, 202
 - cardiac asthma, 213

*Asthma, bronchial—continued**differential diagnosis—continued*

diagnostic aids in differential diagnosis of bronchial asthma

latent wheezing, 176

nasal eosinophilia, 181

response to medication, 180

other diagnostic aids, 180

dust bronchitis, 205

emphysema

congenital lobar, 206

generalized obstructive of infancy, 202

pulmonary, 221

fibrocystic disease, 204

foreign body

Azygos vein shadow mistaken for, 195

in esophagus, 191

in tracheo-bronchial tree, 190

heart disease, congenital, 214

post-encephalitis hyperpnea, 215

pressure on tracheo-bronchial tree

anomalous vessels, 211

adenopathy, 211

echinococcus cysts, 211

sighing dyspnea, 214

stridor, laryngeal

congenital, 183

exudative, 185

neurogenic, 185

tetanic associated with moniliasis, 186

thymic, 209

differences between infantile and adult, 180

emphysema, early appearance in, 179

fever in, 179

management of the child with chronic

asthma, 260

climatotherapy, 475

education, 262

environmental control, 260

Home for Asthmatic Children,

Jewish National, 475

pets, animal, 262, 512

physiotherapy, 263

status asthmaticus, 249

definition, 249

*Asthma, bronchial—continued**status asthmaticus—continued*

treatment

ACTH, 253

bronchoscopy, 256

cortisone, 253

ether in oil, 256

ethyl alcohol, intravenous, 252

fluids, importance of in, 249

oxygen, 256

procaine, intravenous, 257

steroid, 253

treatment of acute attack, 237

aminophylline suppositories, 243

bed rest, 237

cough mixtures, 238

ephedrine, 243

epinephrine

aerosol, 244

injections of, 245

nose drops, 239

steam inhalations, 242

Asthmatic bronchitis, 188

Asthmatic Children, Jewish National Home for, 475

Asthmatic pseudo-rickets, 221

Atelectasis, 221

Atopic dermatitis, 93

age of onset, 5

body build, 94

camp and the child with, 487

characteristics, general of the child with, 93

chronic, 97, 98

complications of, 127

anemia, 141

cataract, 378

death, sudden, 137

dentition, 94

diarrhea, 94, 133

eczema herpeticum, 129

eczema vaccinatum, 128

erysipelas, 132

fever, 123, 134

glomerulonephritis, 133

impetigo, 127

infection, respiratory, 133

nephritis, glomerulo-, 133

Atopic dermatitis—*continued*complications of—*continued*

Kaposi's varicelliform eruption,
129, 140

measles, 14

pyrexia, 122, 134

streptococcal infections, 132

by contact, 105

electrolytes, 95

eosinophilia, 141

focal infection as cause, 165

gastric secretion, 94

histamine in, 95

inhalant allergens in, 105

morbidity and mortality of, 139

phenylpyruvic oligophrenia (ketonu-
ria) and, 134

progression of into asthma, 7

upper respiratory disorders, 7

treatment

general measures

ACTH, 124

cortisone, 124

dietary, 463

environmental control, 108, 510

Fowler's solution, 122

general principles, 108

local measures

bathing, 111

fundamental principles, 108

gentian violet, 116

hydrocortisone ointment, 122

Lassar's paste, 120

one-two-three ointment, 109

resorcin ointment, compound,
121

Rosen's ointment, 109

soap substitutes, 112

Swartz ointment, 122

tar, 117

white, 120

use test in, 110

vioform, 121

wet dressings, 115

x-ray, 122

Atopic erythroderma, 101

Autonomic familial dysfunction, 82

Ayerza's disease, 216

Azygos vein and fissure, 195

B

BAL, 161

Baths in atopic dermatitis, 111

Bedding, 504

Biogenetic relationships (foods), 439

"Bird face," 413

Blood vessels, anomalous, causing dys-
pnea simulating asthma, 211

"Bowen's salute," 305

Bradford postnasal swab, 181

Breast milk, human

drugs, transmission through, 440

foreign proteins, transmission through,
438

hypersensitivity to, 436

pollen transmission through, 440

Bronchiectasis, 404

Bronchitis, asthmatic, 189

Bronchitis, capillary, 202

Bronchitis, dust, 205

Bronchiolitis, 202

Bronchoscopy

in laryngeal stridor, 186

in status asthmaticus, 256

Bronchotetany, 217

Bronchus, foreign body in, 190

Buckwheat, 502

"Bunny nose," 305

Burow's solution, 115

Butter substitute, 452

C

Camp and the allergic child, 438

Canker sores, 402

Capillary bronchitis, 202

Capillary microscopy, 16

Cardiac asthma, 213

Carina, pressure on causing dyspnea
simulating asthma, 211

Cataract, 378

Celiac syndrome, 78

Certification of pediatric allergists, xi

Chilitis, 85

Circumanal contact dermatitis, 86, 159

Circumoral contact dermatitis, 84

Circumscribed neurodermatitis, 169

Clausen tar extract, 120

Climate, 475

California, 478

Climate—*continued*

Denver, 475, 479

El Paso, 478

Florida, 478

Mexico City, 479

Ohio, 477

Pennsylvania, 477

Pittsburgh, 477

Tucson, 476

West Virginia, 477

Clubbing of fingers, 404

Coal tar, 117

Cold, allergy to, 380

Colic, 60

evidence of allergic origin, 61

treatment of, 64

Colitis, chronic ulcerative, 70

incidence of, 71

food allergy as a cause of, 73

treatment of, 73

Collagen diseases, 409

dermatomyositis, 422

lupus erythematosus, 417

polyarteritis (periarteritis nodosa),
414

rheumatic fever, 410

rheumatoid arthritis, 411

scleredema, 421

sclerosis, progressive systemic, 420

Collapse of lungs, massive, 221

Contact dermatitis, 157

ammoniacal (diaper) dermatitis, 158

circumanal, 86, 159

circumoral, 84

patch tests, 157

rhhus toxicodendron (poison ivy), 162

Contactants

foods, 158

metals, 161

poison ivy, 162

quinine, 159

rhhus toxicodendron, 162

stool, 86, 159

treatment, 161

urine, 158

Convulsions (*See also* Epilepsy)

pertussis immunization and, 491

aminophylline and, 250

Corn starch baths, 111

Corticotropin (*See also* ACTH), 266Cortisone (*See also* specific diseases),
266Coryza (*See also* Recurrent upper res-
piratory disorders), 299

Costen's syndrome, 86

Cottonseed, avoidance of, 512

Cough, allergic, 218

Cough mixtures, 238, 239

Cow's milk, 444

allergy to

incidence of, 445

severe, 446

in a walrus, 448

chemical composition of, 444

galactosemia, 449

substitutes for, 452

animal milks

ass, 458

goat, 457

mare, 459

others, 459

meat base milks, 459

soy bean milk, 454

non-animal milks

almond, 459

cereal, 459

nut, 459

poppyseed, 459

taro, 459

transmission of foreign proteins
through, 441

Cryoglobulinemia, 380

Cyclic vomiting, 82, 365

Cystic fibrosis of the pancreas, *See*
Fibrocystic disease

D

Deafness, 229

Death related to

asthma, 226

atopic dermatitis, 137

cold allergy, 385

food allergy

breast (human) milk, 436

cow's milk, 447

soy bean milk, 437

insect bites and stings, 369

Death related to—*continued*

- penicillin, 326
- skin testing, 32
- swimming (bathing), 385
- vaccine injections, 330

Death from allergic shock, post-mortem diagnosis of, 138

Demerol

- in colic, 64
- in asthma, 247

Dentofacial anomalies, 307

Dentition in atopic dermatitis, 94

Depigmentation in atopic dermatitis, 146

Dermal-respiratory syndrome, 73, 94, 425

Dermatomyositis, 422

Dermatophytic lymphadenitis, 102

Dermatitis, atopic, *See* Atopic dermatitisDermatitis, contact, *See* Contact dermatitisDermatitis, seborrheic, *See* Seborrheic dermatitisDermatoses, allergic (*See also* specific diseases), 90Dermatoses, eczematoid (*See also* specific diseases), 166

Detergents, 112

Dietary treatment of allergic disease, 436

- elimination diets, 463
- fatty acids, unsaturated, 469
- rotary diversified diet, 471
- vitamins, 466

Dimercaprol, 161

Diphtheria, 489

Drug allergy, 321

- definition, 321
- hypersensitivity, definition of, 321
- idiosyncrasy, definition of, 321
- incidence of, 322
- prevention of, 339
- side reactions, 322
- specific drugs, 323
 - anesthetics, local, 340
 - atropine, 324
 - aspirin, 324
 - antihistamines, 335
 - codeine, 324

Drug allergy—*continued*specific drugs—*continued*

- insulin, 329
- penicillin, 325
- phenobarbital, 324
- vaccines, *See* specific diseases

Dust bronchitis, 159

Dust free bedroom, 511

Dust, house, *See* House dust

E

Echinococcus cysts simulating asthma, 211

Eczema (*See also* Eczematoid dermatoses)

- allergic, 93
- definition, 93
- infantile, 93
- simple, 93
- herpeticum, 129
- vaccinatum, 128

Eczematoid dermatoses, 166

Eczematoid dermatitis, infectious, 166

Egg, addition of to infant's diet, 496, 502

Electroencephalography, 354

Electrolytes in

- asthma, 201
- atopic dermatitis, 95

Elimination diets, 463

Emphysema

- congenital lobar, 206
- generalized obstructive of infancy, 202
- mediastinal, 223
- subcutaneous, 223
- unilateral obstructive, 178
- pulmonary, 221

Environmental control, directions for, 510

Enuresis, 401

Eosinophil depression test, 275

Eosinophilia

- general considerations, 274
- in atopic dermatitis, 141
- in nasal smears, 303
- stain for (Hansel), 303
- in stools, 76, 80

Eosinophilic pneumonopathy, 387

Eosinophilic pneumonopathy—*continued*
 Löffler's syndrome, 387
 tropical eosinophilia, 389
 Ephedrine, 241
 nose drops, 240
 Epidermoids, directions for avoidance of
 cow hair, 513
 feathers, 512
 goat hair, 514
 hog hair, 513
 horse hair, 513
 pets, 512
 rabbit hair, 515
 Epilepsy, 356
 abdominal, 364
 prophylactic immunizations in, 491
 Epinephrine
 inhalation (aerosol), 244
 injection, 244
 in oil, 246
 poisoning, 257
 Erythema multiforme, 317
 Erythema neonatorum, 52
 Erythema nodosum, 318
 Erythroblastosis fetalis, 279
 Erythroderma, atopic, 101
 Erythrodermia desquamativa, 154
 Erysipelas, 132
 Esophagus, foreign body in simulating
 asthma, 191
 Ethyl alcohol, intravenous in asthma,
 252

F

Facies, allergic, 304, 305, 307
 Familial autonomic dysfunction, 82
 Fatty acids, unsaturated, 469
 Favism, 396
 Fetal hiccoughs, 51
 Fever
 in asthma, 179
 in atopic dermatitis, 123, 134
 Fibrocystic disease, 204
 Fiedler's (isolated) myocarditis, 408
 Focal infection in atopic dermatitis, 165
 in bronchial asthma, 228, 229
 Foods (*See also* individual foods)
 biogenetic relationships, 439
 death from allergy to, 436, 437, 447

Foods—*continued*

egg, method of adding to diet, 496
 introduction of new foods, effect of
 early, 503
 following acute gastrointestinal epi-
 sodes, 504
 polysaccharides, 503
 sensitization acquired by over in-
 dulgence to, 504
 vitamins, 464, 468
 Food dislikes, 12
 milk, 13
 Foreign body
 Azygos vein shadow mistaken for, 195
 in bronchus, 190
 in esophagus, 191
 Fowler's solution, 122
 Fungal dermatoses, 165
 Furniture, 504

G

Galactosemia, 449
 Gamma globulin, 236, 300
 Gastric secretion, 94
 Gastrointestinal allergy, 55
 angioedema, 86
 aphthous ulcerations, 402
 celiac syndrome, 78
 chilitis, 85
 circumanal contact dermatitis, 86, 159
 circumoral contact dermatitis, 84
 colitis, chronic ulcerative, 70
 cyclic vomiting, 82
 geographical tongue, 88
 gingivitis, 85
 intussusception, 86
 pain, 56
 pylorospasm, 67
 pyloric stenosis, hypertrophic, 67
 regional enteritis, 87
 roentgenological evidence of gastro-
 intestinal allergy, 57
 Genitourinary allergy, 295, 400
 enuresis, 401
 vulvo-vaginal pruritis, 295
 Gentian violet, 116
 Geographical tongue, 83
 Gingivitis, 85

Glomerulonephritis
 in atopic dermatitis, 133
 in Schönlein-Henoch purpura, 346
 Goat's milk, 457

H

Hansel stain, 303
 Hay fever, *See* Pollinosis
 Heart disease
 asthma and, 224
 cardiac asthma, 213
 congenital, 214
 myocarditis, 408
 Hematuria, idiopathic, 347
 Herpes simplex, *See* Eczema herpeticum
 Hiccoughs, fetal, 51
 Hill scarifier, 33
 Hip joint, transient synovitis of, 399
 Histamine
 in atopic dermatitis, 95
 in physical allergy, 384
 History taking, 19
 Hives, *See* Urticaria
 Home for Asthmatic Children, Jewish
 National, 475
 House dust
 in atopic dermatitis, 106
 avoidance of, 511
 humidity and, 477
 season of, 304
 Human breast milk, *See* Breast milk,
 human
 Hydrocortisone, 271
 Hydrocortisone ointment, 122, 171
 Hyperpnea, post-encephalitic, 215

I

Ileitis, regional, 87
 Impetigo, 127
 Infant feeding, early introduction of
 new foods, 503
 India gum, 517
 Infection (*See also* specific disease)
 intercurrent and allergic disease, 14
 Infectious eczematoid dermatitis, 166
 Inhalant allergens (*See* Osmyls and spe-
 cific allergen)
 in atopic dermatitis, 105
 Insect bites and stings, 369

Insect bites—*continued*
 death from, 370
 prophylaxis of, 315, 370
 symptomatology, 369
 treatment, 371

Intrauterine phenomena related to al-
 lergy
 fetal hiccoughs, 51
 reagins in umbilical cord blood, fail-
 ure to demonstrate, 50
 sensitization, 49, 50
 Intussusception, 86
 Ipecac, 239
 Isolated (Fiedler's) myocarditis, 408
 Iritis, 378

J

Jewish National Home for Asthmatic
 Children, 475

K

Kapok, avoidance of, 512
 Kaposi's varicelliform eruption, 129, 140
 Karaya gum, avoidance of, 517
 Kartagener's syndrome, 406
 Keratitis (eye), 377
 Kerato-conjunctivitis, 378

L

Landau nasal aspiration, 240
 Laryngeal stridor, 183
 Lassar's paste, 120
 Leiner's disease, 154
 Letterer-Siwe's disease, 150
 Lips, contact dermatitis of, 85
 Liquor carbonis deturgens, 111
 Lobar emphysema, congenital, 206
 Löffler's syndrome, 387
 Lupus erythematosus, 417
 Lymphoid tissue of nasopharynx, recur-
 rent, 229

M

Mare's milk, 458
 Marriage between allergic individuals.
 494
 Massive collapse of lungs, 221
 Measles
 atopic dermatitis and, 14, 95

- Measles—*continued*
 prophylaxis of, 505
 treatment of, 505
 Meat base milks, 459
 Meningitic serum reactions, 352
 Menthol, 242
 Migraine, 360
 age of onset, 360, 361
 differential diagnosis, 364
 cyclic vomiting and, 364
 characteristics in childhood, 363
 heredity in, 360
 prognosis, 364
 psychogenic factors, 362
 treatment, 366
 Milk (*See* specific animal)
 Milk, breast, human (*See* Human breast milk)
 Milk, cow (*See* Cow's milk)
 Milks, others (*See* Cow's milk, substitutes for)
 Monilia infection, 167
 parathyroid tetany complicating, 186
 Mucoviscidosis, 204
 Mumps, *See* Parotitis, allergic
 Myocarditis, isolated (Fielder's), 408

N

- Naphthalan (naftalan), 118
 Nasal obstruction, 239, 242
 Nasal smears
 staining (Hansel), 303
 technic of making, 181
 Nephritis
 in atopic dermatitis, 133
 in Schönlein-Henoch purpura, 346
 Neuroallergy (*See also* specific diseases), 350
 electroencephalography, 354
 epilepsy, 356, 364
 meningitic serum reactions, 352
 migrane, 360
 rabies, 333, 352
 Neurodermatitis, circumscribed, 169
 Newborn
 erythema neonatorum, 52
 prophylaxis of allergic disease, 493
 skin tests in, 40
 urticaria, 51

- Nose drops, 239, 308
 Nummular eczema, 169

O

- Oatmeal baths, 111
 Ocular allergy, 376
 cataract, 378
 conjunctivitis, 376
 iritis, 378
 keratitis, 377
 kerato-conjunctivitis, 377
 uveitis, 378
 vernal conjunctivitis, 376
 Odors (*See also* Osmyls), 261
 Oleoma, 246
 Oleomargarine, 452
 Ophthalmic testing, 41
 Orange, 502
 Orthodontia, 307
 Osmyls, 439, 504
 urticaria from, 311

P

- Pain, abdominal (*See also* specific diseases), 55, 56
 Pancreas, fibrocystic disease of, 204
 Parotitis, allergic, 402
 Passive transfer tests, 39
 Peanut, 94, 246, 502
 Pediatric allergy
 certification in, xi
 clinics, early, x
 differences from adult allergy, vii
 history of development of, ix
 Penicillin, 325
 death from, 326
 skin test with, 327
 Perianal dermatitis, 86, 159
 Periarthritis nodosa, 414
 Pertussis
 asthma and, 490
 convulsions and, 491
 immunization against, 491
 Pets, animal, 262, 512
 Pharyngitis, granular, 230
 Phenol, sensitivity to, 47
 Phenylpyruvic oligophrenia (ketonuria), 134

Physical allergy, 380
 cold hyposensitization, 383
 histamine injections for, 384
 Physical examination, 25
 Physiotherapy in bronchial asthma, 263
 Pica, 20
 Pneumothorax, 223
 Poison ivy, 162
 Poliomyelitis and injections, 492
 Pollinosis, 280
 camping and, 485
 dermatitis due to, 296
 incidence of, 280
 masked pollinosis, 283
 skin testing, 284
 symptomatology, 281
 toxemia due to, 297
 treatment, specific, 285
 symptomatic, 290
 indications for, 282
 urticaria, due to, 296
 vulvo-vaginal pruritis, 295
 Polyarteritis, 414
 Poppyseed milk, 459
 Post-encephalitis hyperpnea, 215
 Post-mortem diagnosis of allergic death,
 138, 373, 385
 Potassium in steroid therapy, 272
 Potassium iodide, 252, 269
 Potassium mixture (A-B-C), 269
 Potassium permanganate, 115
 Prednisone, 276
 Prednisolone, 276
 Pregnancy
 diet in for prophylaxis of allergic
 disease, 495
 steroid therapy in, 278
 Proetz position, 240
 Procaine, intravenous for treatment of
 asthma, 257
 Propadrine, 238, 241
 Prophylaxis of allergic disease, 493
 feeding of newborn, 493
 feeding of the older infant, 502
 prenatal care, 495
 Prophylactic immunizations, routine in
 allergic children, 489
 Pseudo-rickets, asthmatic, 221
 Psoriasis, 147, 155, 171

Psychosomatics, 425
 maternal introjection, 433
 maternal rejection, 428, 429
 Purpura, idiopathic, thrombocytopenic,
 342, 348
 Purpura, Schönlein-Henoch, 342
 Pyloric stenosis, hypertrophic, 67
 Pylorospasm, 67
 Pyrethrum, avoidance of, 518

R

"Rabbit nose," 305
 Rabies, 333, 352
 Red babies, 103
 Reference texts, suggested, 518
 Regional enteritis, 87
 Resorcin ointment, 121
 Respiratory disorders, recurrent, upper,
 299
 differential diagnosis, 300
 treatment
 specific, 307
 symptomatic, 308
 Rheumatic fever, 410
 Rheumatoid arthritis, 411
 Rhinitis perennial allergic, 299
 dental anomalies in, 307
 hypothyroidism as cause, 308
 treatment
 specific, 307
 symptomatic, 308
 Rhus toxicodendron, 162
 Ribs, spontaneous fracture of, 225
 Rickets, asthmatic pseudo-, 221
 Rose fever, *See* Pollinosis
 Rotary diversified diet, 471

S

Schönlein-Henoch syndrome, 342
 allergy as cause of, 346
 food, 346
 other allergens, 347
 exanthem in, 343
 gastrointestinal symptoms, 344
 nephritis, 346
 Scleroderma, generalized, 420
 Scleredema, 421
 Sclerema neonatorum, 421
 Scleroma, 421

- Sclerosis, progressive systemic, 420
- Seborrheic dermatitis, 143
- differential diagnosis, 144
 - forms of, 143
 - relationship to atopic dermatitis, 144
 - relationship to psoriasis, 147
 - treatment, 150
- Selenium sulfide, 152
- Sensitization, intrauterine, 49
- Silk, directions for avoidance of, 513
- Silk floss, 512
- Sighing dyspnea, 214
- Skin tests, 28
- allergens to be tested, 37
 - antihistamines in, 39
 - characteristics in infants, 29
 - clearing of skin for, 40
 - in newborn, 40
 - intradermal tests, 35
 - common errors in, 36
 - death from, 32
 - passive transfer tests, 39
 - technic of, 44
 - negative tests with clinical sensitivity, 29
 - positive tests, significance of, 29
 - positive tests in non-allergic individuals, 28
 - preparation of child for skin tests, 30
 - scratch tests, 31
 - common errors in, 35
 - death from, 32
 - technic of, 33
- Smallpox vaccination, 492
- Soap, substitutes for, *See* Detergents
- Sodium sulfacetamide, 151
- Soy bean milk, 453
- preparation of home made, 455
- Status asthmaticus, 249
- Steam inhalations, 242
- Steroid treatment of allergic disease (*See also* specific disease, specific steroid), 266
- adverse reactions, 271
 - choice of drug, 268
 - indications for, 267
 - general procedures, 268
 - potassium in steroid therapy, 272
 - in pregnancy, 278
- Stomatitis aphthous (ulcerative), 402
- Sulfonated oils, 112
- Swartz ointment, 122
- Swimming, 385, 487
- Synovitis of the hip joint, transient, 399
- T
- Tar, 117
- Tar baths, 111
- Taro base milk, 459
- Tension-fatigue syndrome, allergic, 392
- Tetanus antitoxin
- bovine, 490
 - horse (despeciated), 490
- Tetany, laryngeal, hypoparathyroid, 186
- Texts, references, suggested, 518
- Thorn test, 275
- Thymic asthma, 209
- Thyroid, 15, 308
- Tonsils in relationship to asthma, 228
- Treatment of patient by referring physician, 46
- Tropical eosinophilia, 389
- Tuberculosis and asthma, 225
- Twins, identical, allergy in, 16
- Typhoid immunization, 485
- U
- Ulcerative (aphthous) stomatitis, 402
- Ulcerative colitis, chronic, 70
- Upper respiratory disorders, recurrent, 299
- Urticaria and angioedema, 311
- altitude, 481
 - facititia, 315
 - gastrointestinal, 55
 - infectious, 312
 - newborn, 51
 - papular, 314
 - physical allergy as cause of, 312
 - pigmentosa, 316
- Use test, 110
- Uveitis, 378
- V
- Vaccines, allergy to, 330
- Vascular anomalies and wheezing, 221
- Vernal conjunctivitis (catarrh), 376
- Vioform, 121, 128, 151

Vitamins, 466, 468

in elimination diets, 466

in feeding of potentially allergic infants, 503

Vulvo-vaginal pruritis, 295

W

Walrus, allergy to cow's milk in, 448

Whipped cream, substitute for, 452

Wood tar, 117

Wool, sheep, 105

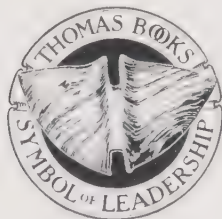


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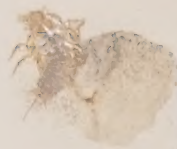
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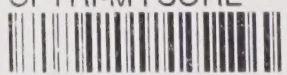
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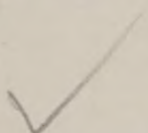


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